Copper Mediated, Transmetallation Coupling Reactions using High Intensity Ultrasound

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ABSTRACT

This dissertation summarizes research efforts focused on the use of boron and copper acetate to form new carbon-carbon and carbon-heteroatom bonds. Two new methods were developed using high intensity ultrasound as the reaction energy source. The first focused on the homocoupling of various aryl compounds using a commercially available polymer support. The use of this polymer support allows the reaction to proceed in an aqueous solvent system with only minimal preparation. The product yields were better than values reported in the literature using traditional reaction conditions and reaction times were decreased from 24-72 hours to 6 hours. The second method involved the application of ultrasound irradiation to the Chan-Evans-Lam reaction for the O-arylation of phenols, N-arylation of anilines and indoles, and S-arylation of thiols. The application of ultrasound to the Chan-Evans-Lam reaction decreased the reaction time from 72 hours to 4 hours while improving the product yield an average of 20% over reported results.

Reactions from both methods were expanded successfully from the millimole scale to the gram level while maintaining good product yields indicating potential applications in industrial processes. A mechanism study indicated that the two methods are related in that there was a similar transformation of the copper salt. Comparing these study results to literature reports suggests that the methods involve an oxidative addition / reduction elimination mechanism similar to the classic Ullmann reaction. The methodology of the research described herein can be characterized as atom efficient,

scalable, environmentally friendly, inexpensive, and capable of rapidly producing high yields of the desired products.

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SYMBOLS

°	degrees
))))	ultrasound
Δ	delta (heat)
δ	delta (ppm shift)
θ	theta
σ	sigma
A	Angstrom
C	centigrade
eq	equivalents
g	grams
Hz	Hertz
MHz	megahertz
min	minutes
mg	milligrams
ml	milliliters
mmol	millimolar
N	normal
r.t.	room temperature

ABBREVIATIONS

aq	aqueous
Ar	Aryl
BF_3	trifluoroborate
$B(OH)_2$	Boronic Acid
Br	Bromine
BR_2	Organoborate
C	Carbon
$CaCO_3$	Calcium Carbonate
$CDCl_3$	Deuterated Chloroform
CF_3	Carbontrifluoride
CH_2Cl_2	Dichloromethane
Cl	Chloride
CN	Nitrile
^{13}CNMR	^{13}Carbon Nuclear Magnetic Resonance
CO_2R	Ester
Cu	Copper
$CuCl_2$	Copper(II) Chloride
CuCN	Copper(I) Cyanide
CuI	Copper(I) Iodide
$CuNO_2$	Copper(II) Nitrate
Cu_2O	Copper Oxide

$Cu(OAC)_2$	Copper(II) Acetate
$CuSO_4$	Copper(II) Sulfate
$CsCO_3$	Cesium Carbonate
d	doublet
DCM	Dichloromethane
dd	doublet of doublets
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl Sulfoxide
dq	doublet of quartets
ESI	Electron Spray Ionization
Et_3N	Triethylamine
EtOH	Ethanol
Fe	Iron
gc/ms	Gas Chromatograph / Mass Spectrometer
H	Hydrogen
H_2O	Water
^{1}HNMR	^{1}Hydrogen Nuclear Magnetic Resonance
I	Iodide
J	Proton-proton coupling constant
K	Potassium
KOH	Potassium Hydroxide
Ln	Ligand

M^+	Metal
M-1	Mass minus one
M+1	Mass plus one
Me	Methyl
m	multiplet
ms	Mass Spectrometry
N	Nitrogen (amine)
$Na^{123}I$	Sodium Iodide 123
NaOH	Sodium Hydroxide
NH	Amine
Ni	Nickel
NMR	Nuclear Magnetic Resonance
N_2	Nitrogen gas
NO_2	Nitrate
Pd	Palladium
$PdCl_2$	Palladium Chloride
pXRD	Powder X-Ray Diffraction
O	Oxygen
OH	Hydroxyl
q	Quartet
R	Substitutent
S	Sulfur

SCN	Thiocyanate
Sn	Tin
t	triplet
THF	Tetrahydrofuran
TMS	Tetramethylsilane
X	Halide
Y	Substituent
Zn	Zinc

CHAPTER I

TRANSMETALLATION WITH BORON IN ORGANIC CHEMISTRY

1.1 Scope of this Dissertation

This dissertation is focused on the coupling reactions of organoborates using ultrasound as the energy source and a copper salt. To determine the scope of the newly developed method, a series of experiments were designed and completed. These experiments were used to evaluate the coupling of an arylborate in: (1) homocoupling reactions; (2) the coupling reaction of arylborates with phenol based compounds; (3) the coupling reaction of arylborates with aniline based compounds; and (4) the coupling reaction of an arylborate with thiol based compounds. Each chapter will illustrate the synthetic utility of the new method, describe relationships with published literature, and discuss relevant mechanistic interpretations. The current chapter highlights appropriate background information that is necessary for understanding the chemistry discussed in this dissertation.

1.1.1 Historic Aspects of Transmetallation in Organic Synthesis

The reaction of a transition metal with an organic compound containing a semi-metal (B, Si, Bi, Sn) historically revolves around the transfer of the organic constituent from the semi-metal to the transition metal, often referred to as transmetallation. The first use of transmetallation in organic synthesis occurred in the early 1900s with the development of the Grignard and Ullmann reactions.[1] The Ullmann reaction is of particular interest as it uses an oxidation addition / reduction elimination mechanistic pathway to couple organic molecules.[1] This oxidative addition / reductive elimination

mechanism, combined with transmetallation, became popular in the 1970's with the development of several named reactions; including the Negishi, Sonogashira, Stille, and Suzuki reactions.[1] These reactions have become important to synthetic chemists as they provide the structural motifs necessary for a wide range of fundamental building blocks.[2]

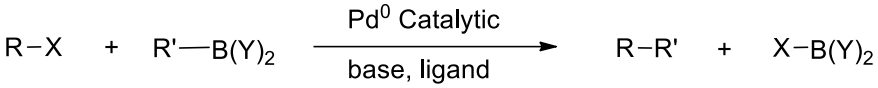
Even though the Ullmann, Negishi, Sonogashira, Stille, and Suzuki reactions are all important tools for the organic chemist, they are not free of negative aspects: the Negishi, Sonogashira, Stille, and Suzuki reactions are only applicable to carbon-carbon coupling and, although the Ullmann can be used to couple carbon to nitrogen, sulfur and oxygen (addition to carbon-carbon), the related harsh conditions preclude its use in many fragile molecules.[1-2] In the early 2000's, several investigators were able to circumvent some of the negative aspects of the reactions, when they developed methods for coupling carbon to a variety of heteroatoms using mild reaction conditions, and producing modest product yields.[2a, 3]

1.1.2 Reactions of Transmetallation in Organic Synthesis

Transmetallation has been used in organic synthesis for well over 100 years and has been instrumental in an exceptional number of reactions.[1, 4] Within this broad array of methods is a set of reactions that use a metal catalyst to achieve a coupling reaction. Two of the more commonly used coupling reactions are the Suzuki and Ullmann reactions. Both require the use of an aryl halide but the Suzuki uses an organoborate and mild reaction conditions as compared to the Ullmann reaction that requires harsh conditions but can be used to couple the aryl halide to a heteroatom (**Scheme 1-1**).

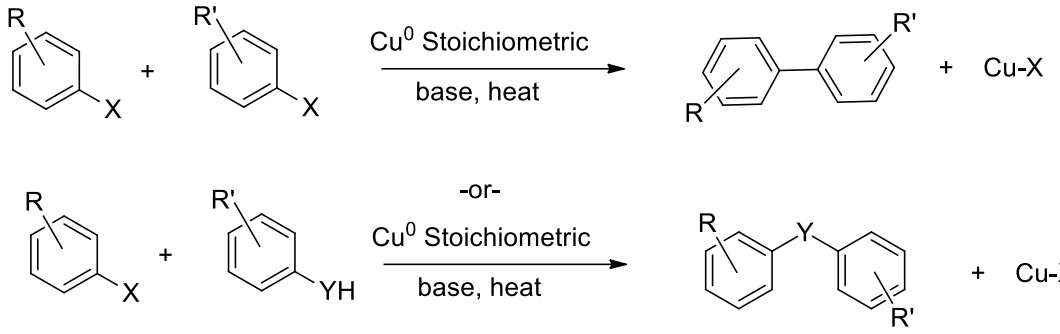
Scheme 1-1 Coupling by either Suzuki-Miyaura or Ullmann Reaction [1-2, 5]

Suzuki-Miyaura Coupling Reaction



R = alkenyl, aryl, alkyl; R' = alkyl, allyl, alkenyl, alkynyl, aryl; Y = alkyl, OH, O-alkyl
X = Cl, Br, I, OTf, $OPO(OR)_2$ (enol phosphate)

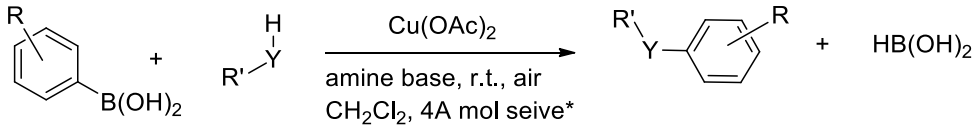
Ullmann Coupling Reaction



R, R' = alkenyl, aryl, alkyl, H, CN, NO_2, CO_2R, I, Br, Cl;
X = I, Br, Cl, SCN;
Y = NH, O, S

In 1998, the Chan-Evans-Lam Modified Ullmann Condensation Reaction was developed. This reaction takes elements of the Suzuki and Ullmann reactions, and applies them to the coupling of arylborates and heteroatoms, under mild conditions, using a copper salt, and producing modest product yields (**Scheme 1-2**).[3d, 6]

Scheme 1-2 Chan-Evans-Lam Modified Ullmann Condensation Reaction [3d, 3e, 6b, 7]



R and R' = virtually any substituent; Y = N, O, S, Se, Te, Cl, Br, I
*the 4A mol seive was not initially reported however subsequent publications indicate water can not be present during the reaction

1.1.3 Reactions of Copper using Ultrasound in Organic Synthesis

Ultrasound in organic and organometallic synthesis has been used historically for improving reactions. Ultrasound typically allows the use of less hazardous chemicals and solvents, decreased energy consumption, improved product selectivity, and improved product yields.[8] When ultrasound is introduced to a liquid surface, the liquid will absorb a portion of the generated vibrational energy. If the amplitude of the vibration is too great for the liquid, the liquid will be broken into large chunks and be ejected at high velocity – a phenomena known as cavitation.[9] As cavitation occurs, micro-sized bubbles are created in the wake of the liquid jet.[10] Subsequent cavitations will cause the generated bubbles to collapse, with the result of significant amounts of energy being released - an estimated several thousand degrees Kelvin and hundreds of atmospheres of pressure in the immediate vicinity of the collapse.[11] This heat and pressure can easily translate to energy to be used in the chemical reaction.[10]

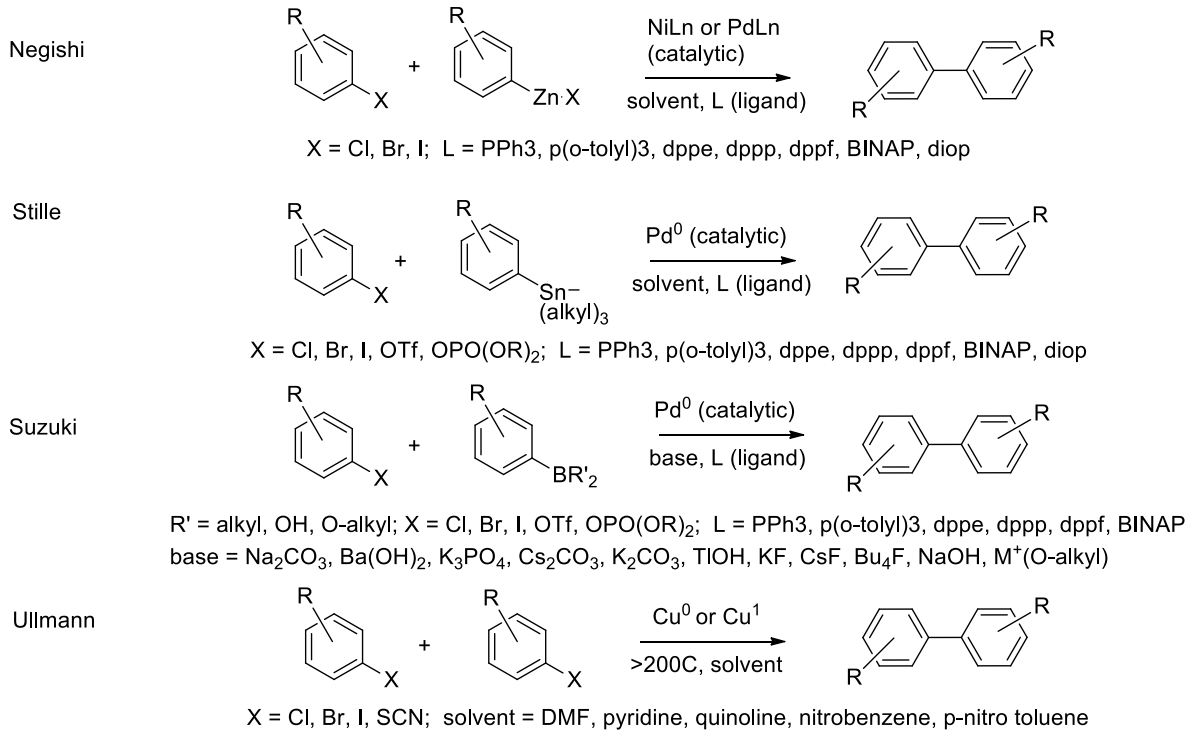
Ultrasound is known to improve reactions involving metals or metal salts. The microjects and cavitations clean oxide layers from a metal surface, promote mass transport, or fragment larger particles and crystals to a nano-sized material (increasing surface area for enhanced reactivity).[10, 12] In this dissertation, ultrasound has been

applied to both the Suzuki and Ullmann reactions with improved results (decreased reaction times, decreased metal requirements, increased product yields); however, ultrasound has not been applied to the Chan-Evans-Lam reaction.[10, 13]

1.2 Homocoupling of Aryl Compounds

The homocoupling of aryl compounds is an important reaction used in the formation of fundamental building blocks for numerous applications. There are several reactions that have been used to achieve such coupling. Some of the more popular reactions include the Negishi, Stille, Suzuki, and Ullmann reactions.[1] Each of these reactions requires the use of a transition metal to facilitate an aryl homocoupling (**Scheme 1-3**):

Scheme 1-3 Aryl Homocoupling[1]



All of these reactions have significant negative aspects associated with them. The Negishi and Stille coupling reactions both produce a highly toxic metal halide byproducts. The Stille and Suzuki reactions require the use of an expensive palladium catalyst. Although the Ullmann reaction uses relatively safe and inexpensive copper, it requires stoichiometric quantities of the metal, along with high heat, and several days of reaction time.[1, 14] Despite these issues, the reactions have been used for the synthesis of various biaryl compounds for many years. Since the development of these reactions, efforts have been undertaken to replace the expensive metals, reduce the toxicity of the generated waste, and improve reaction efficiency. The application of microwave and ultrasound technologies, specifically, has been shown to improve yields and improve

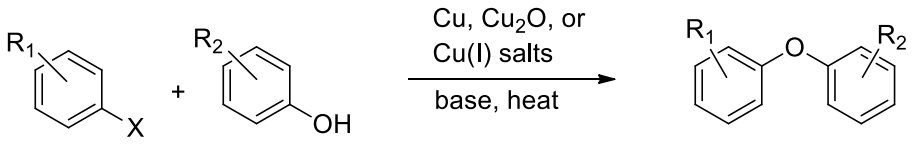
product selectivity in these reactions, while decreasing the reaction times and quantities of metals required for synthesis.[13, 15]

1.3 O-Arylation and N-Arylation of Phenol and Aniline

Diaryl ethers and diaryl amines are structurally important as they provide fundamental building blocks in many modern synthetic reactions. Historically, if the synthesis of diaryl ethers and diaryl amines was to be conducted by a coupling reaction, the Ullmann reaction was the principal route. The coupling of C-O and C-N by this method requires similar conditions to those found in C-C Ullmann coupling reactions.

The Ullmann O-arylation coupling reaction uses a copper oxide or copper(I) salt to couple an aryl halide and phenol, under basic conditions, and high heat for 8-72 hours, depending on the aryl groups (**Scheme 1-4**).[2a, 16]

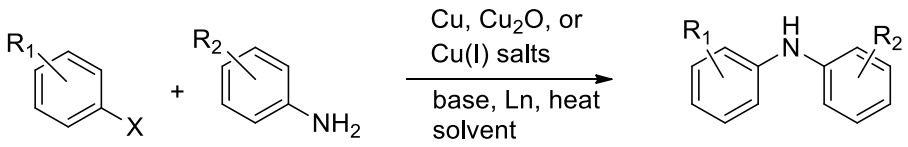
Scheme 1-4 Ullmann O-Arylation of Phenol [1, 16]



X = Br, I; base = Cs_2CO_3, $CaCO_3$, NaOH, KOH; solvent = DMF, DMSO (dry), DCM

The synthesis of a diaryl amine by the Ullmann reaction occurs in a similar manner, and under the same conditions, as the diaryl or diaryl ether reaction (**Scheme 1-5**).[17]

Scheme 1-5 Ullmann N-Arylation of Aniline[1, 17]

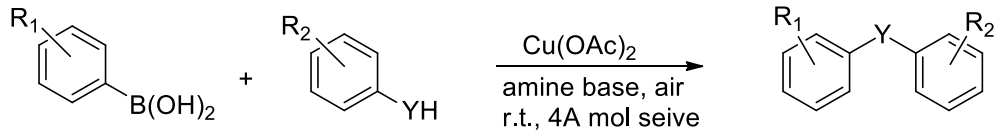


X = Br, I; base = Cs_2CO_3, $CaCO_3$, NaOH, KOH; solvent = DMF, DMSO (dry), DCM

Unfortunately the harsh reaction conditions (high heat, long reaction times, strong basic conditions) can preclude the use of many sensitive molecules in the coupling reaction. With current environmental regulations and metal prices, the consumption of stoichiometric amounts of copper in the Ullmann reaction results in a disposal and cost issue.[1, 16e]

Between 1950 and 1990, several carbon-heteroatom coupling reactions were developed, however most used highly toxic metals (lead, tin, arsenic), with no improvement in product yields. They did provide the pathway for the development of one of the most used cross-coupling reactions: the Chan-Evans-Lam modified Ullmann Reaction.[2a, 6a, 16e] This reaction improves upon the Ullmann recation by using catalytic (or sub-stoichiometric) amounts of copper(II) salt, an arylboronic acid instead of an aryl halide, and is carried out at room temperature (**Scheme 1-6**).[3b, 3d, 6a] The reaction has been reported to be near universally applicable for aryl coupling to various anilines and phenols and produces similar yields (30-80%) in similar reaction times (1-3 days) to the Ullmann reaction, with the only negative aspect being that water poisons the reaction.[2a, 3d, 6b, 7c]

Scheme 1-6 Chan-Evans-Lam Modified Ullmann Reaction [3b, 3d, 6a]



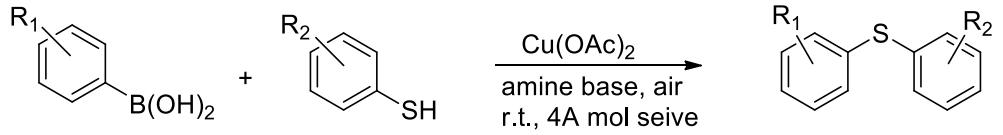
Y = O or NH; R = vitually any substituent

The Chan-Evans-Lam reaction has been applied to numerous coupling reactions, with good success.[7c, 14] To date, microwave and ultrasound technology has only been applied to the traditional Ullmann C-N and C-O coupling reaction in isolated cases; MW and ultrasound have not been reported in the Chan-Evans-Lam reactions.[18]

1.3 S-Arylation Coupling of a Thiol

There are a numerous methods for synthesizing biaryl sulfides; however, for the synthesis of a biaryl sulfide via a coupling reaction, an Ullmann reaction has been required, until recently.[19] There have been a few reports focused on using catalytic amounts of palladium to achieve the C-S coupling reaction, however all other reaction conditions of the Ullmann were required, with no substantial product yield improvements.[20] Like the N- and O- arylation reactions, the conditions of the Ullmann reaction conditions preclude many thiols from being used in the coupling reaction.[7a] Shortly after the development of the Chan-Evans-Lam modified Ullman reaction, it was successfully applied to the S-arylation of thiols (**Scheme 1-7**).[2a, 6b, 7a, 7c]

Scheme 1-7 S-Arylation of Thiols, Chan-Evans-Lam Modified Ullmann Reaction



By coincidence, the use of copper may prevent the competing formation of the related disulfide. During the Ullmann reaction, the metal reaction product is copper(I).[1, 21] Reports have indicated that a copper(I) species will cleave an organodisulfide.[22] It is unknown if copper(I) is produced during the Chan-Evans-Lam reaction. To date, microwave and ultrasound technology has not been applied to the Chan-Evans-Lam modified Ullmann reaction in the S-arylation of thiols.

1.4 Use of Ultrasound in Coupling Reactions

It is known that the use of ultrasound can dramatically improve Suzuki or Ullmann coupling reactions: improved yields and decreased reaction times for both reactions, a 60% reduction in the amount of copper required for the Ullmann reaction, and the Ullmann reaction can be run at "room temperature."[8, 10-12, 13b, 13c, 15] Unfortunately, a survey of the literature revealed that there is no consensus for the use of ultrasound methods in coupling reactions. Most reports involved the use of a water bath ultrasound instead of a direct energy source; additionally, there have been no standards reported for reaction times, amounts of delivered energy, or reaction temperature.

1.5 Statement of Problem

There are several named reactions that can be used for C-C coupling, however they all have significant detrimental aspects. Similarly, there are only two named

reactions that can be used in the carbon-heteroatom coupling reaction, and both require significant reaction times. A new method was developed in the hopes of rectifying some of these negative characteristics.

Experiments were conducted to 1) determine what metals could be applied to homocoupling reactions conducted in an aqueous solvent system using a polymer support; 2) develop an ultrasonic method that could improve this method by decreasing reaction times, decreasing the amount of metal required, and improving product yields; 3) determine the applicability of the homocoupling reaction to arylboronic compounds that are sterically hindered, have electron withdrawing groups, or have electron donating groups; and 4) investigate the mechanism of the new reaction (Chapter 2). The new method was applied to the O-arylation of phenol to determine 1) the effect of ultrasound on the reaction time and product yield; 2) the effect of sterics and electronics of the arylborate on the product yield; and 3) the effect of sterics and electronics of the phenols on the product yield (Chapter 3). The new ultrasound method was applied to the N-arylation of aniline and amine heterocycles to determine 1) the effect of ultrasound on the reaction time and product yield; 2) the effect of sterics and electronics of the arylborate on the product yield; and 3) the effect of sterics and electronics of the anilines on the product yield (Chapter 4). The new method was applied to the S-arylation of thiols to determine 1) the effect of ultrasound on the reaction time and product yield; 2) the effect of sterics and electronics of the aryl-borate on the product yield; and 3) the effect of sterics and electronics of the thiols on the product yield (Chapter 5).

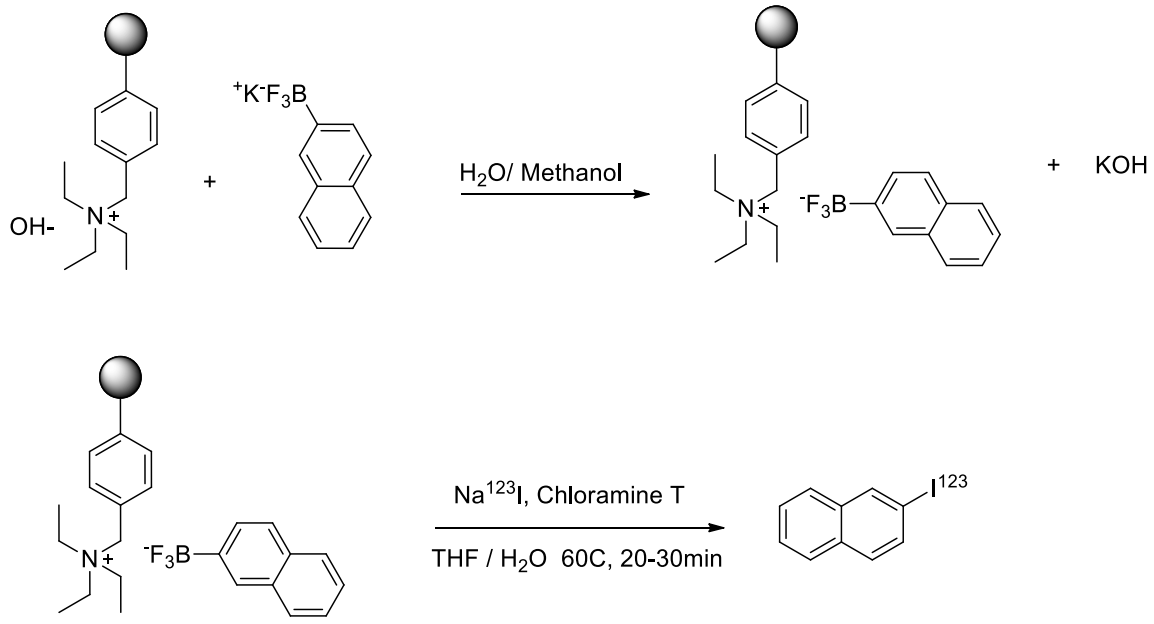
CHAPTER II
HOMOCOUPLING OF POLYMER SUPPORTED ARYLTRIFLUOROBORATES

2.1 Introduction

The homocoupling of aryl compounds is an important reaction used in the formation of fundamental building blocks for numerous industrial and pharmaceutical materials. Unfortunately many of the widely used homocoupling reactions require expensive catalysts (Suzuki, Stille) or use harsh reaction conditions with large quantities of metal (Ullmann) while producing only modest product yields.[13a, 13b] In an attempt to improve the negative aspects of these reactions, researchers have employed a variety of tactics, including the use of different metals, ultrasound or microwave energy sources, various solvent systems, and different ligands; all with varying degrees of success.[5b, 5c, 13a, 13c, 23] Of these reaction modifications, one area that has shown great promise is the use of a polyethylene glycol supports in Suzuki reactions. There are a number of reports that indicate successful synthesis of biaryl compounds using polymer supports; benefits of the modification include successful reactions run in water and under atmospheric conditions with good product yields (attributed to increased metal surface area as the chemical reaction produces palladium nano-particles).[24] Unfortunately many of these reactions require preparation of the polyethylene glycol before it can be used in the reaction.[24]

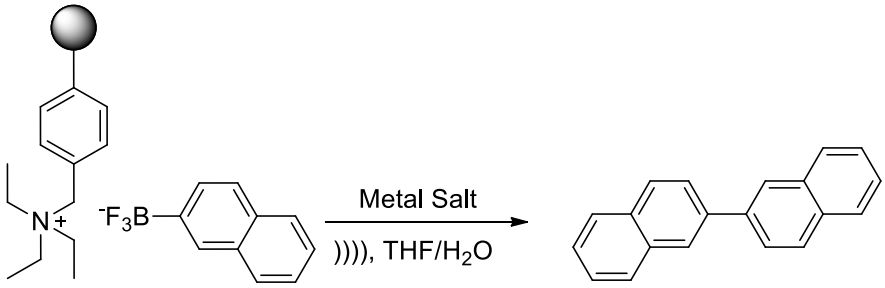
The Kabalka group recently reported on an iodination reaction that used aryl trifluoroborates that were ionically bound to Dowex polymers (**Scheme 2-1**).[25]

Scheme 2-1 Iodination of Naphthalene-Trifluoroborate [25]



Since Dowex is commercially available, and does not require extensive preparation, the Kabalka group attempted a homocoupling reaction, similar to the reported polyethylene glycol methods using Dowex-naphthalene-trifluoroborate complex.[26] Palladium(II) acetate was chosen as the survey metal, following the reported methods.[24, 27] Initial survey reactions using heat and stirring indicated only minimal product yield (7%) after 72 hours. It was decided to carry out the reaction using an ultrasound energy source (in an attempt to improve the reactivity of the metal), this provided a significantly improved yield of 92%, and set forth the initial reaction design (**Scheme 2-2**).[28]

Scheme 2-2 Homocoupling of Ionically Bonded Dowex-Naphthalene-Trifluoroborate[26]



The successful synthesis of 2-2'-binaphthalene, in good yield, supports the postulate that homocoupling reactions could be accomplished using other aryl-trifluoroborate compounds ionically bonded to Dowex.

2.2 Results and Discussion

2.2.1 Method Development

The successful homocoupling of Dowex supported 2-naphthatrifluoroborate prompted a detailed method development for application to the homocoupling of other aryltrifluoroborates. Although a survey experiment showed palladium(II) acetate could be used in the homocoupling reaction, it was decided to investigate other metal salts for applicability in the reaction. Metals were chosen based on a combination of availability, water stability, oxidation state / electronic structure, and reported success in literature. [2b, 3a, 5a-c, 13c, 14, 23a, 29] Reactions were carried out using varying amounts of metals and using the reaction conditions outlined in Scheme 2-2. The results of the survey reactions

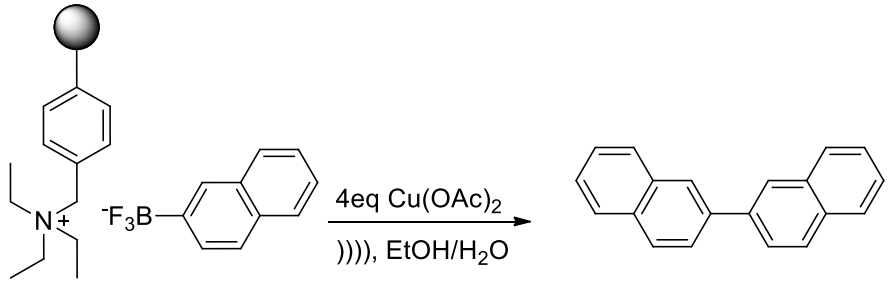
are presented in **Table 2-1**; the equivalents reported are the quantity of metal that provided the highest yields of binaphthalene; these values were confirmed in triplicate reactions and the yields reported are the average of those reactions.

Table 2-1 Comparison of Metal Salts and Binaphthalene Yields

Metal Salt	Yield of Bi-Naphthalene	Equivalents of Metal
Copper(II) acetate dihydrate	56%	4
Zinc acetate dihydrate	10%	3
Nickel(II) acetate tetrahydrate	No reaction	1-4
Iron(II) acetate anhydrous	17%	2
Silver(II) acetate, anhydrous	6%	2
Cobalt(II) acetyl-Acetonate, anhydrous	No reaction	1-4
Palladium acetate	92%	1
Platinum oxide (Adam's catalyst)	10%	2

Copper(II) acetate was chosen for further study because of its low cost, availability, and relation to the Chan-Evans-Lam modified Ullmann reaction. First the solvent system was to be investigated. Since it was desired to keep the system aqueous, only organic solvents that were miscible in water were evaluated. The first solvent chosen, ethanol, showed dramatic yield improvement, 97%. Because of the excellent yield, cost, and environmental nature, no other organic solvent components were investigated (**Scheme 2-3**).

Scheme 2-3 Copper(II) Acetate Based Homocoupling of Dowex-Naphthalene-Trifluoroborate



The next part of this study involved optimization of the ultrasound equipment. A preset 20 kHz horn dismemborator was chosen as it delivers the energy directly to the reactants, with the energy level being known based on the instrument reading.[9] The sonicator used a ½ inch flat probe, titanium alloy tipped horn, with a 2 inch high by 1 inch diameter glass reaction vessel. The ultrasound method was adopted from U.S. Steel Environmental Company, where a one minute cycle of sonication followed by a three second pause (allowing heat dissipation from the probe).[30] The probe tip was placed approximately half way between the surface top and the copper acetate at the bottom of the vessel (this position was within the manufacture recommendations of placing the probe not less than 1 to 1 ½ tip diameters into the solution without touching the vessel). The reaction depicted in Scheme 2-3 was run multiple times while the reaction time and energy (watts) were independently varied, to determine the optimal conditions for each (based on product yield). The reaction times were varied from 1-8 hours, and the energy

varied from 15 to 75 watts. A reaction time of six hours, with a probe power level of 55 watts (corresponding amplitude of 10%), provided the best product yields. Post reaction, the temperature of the solvent system was found to range between 50-70 °C. Although it is recommended to keep the reaction at cold to maximize cavitations, it was decided to complete the reactions without any external cooling for industrial application.[8-9]

Once the reaction conditions were established, copper(II) acetate was re-evaluated to determine if any other copper salt provided improved results (quantity used versus yield of binaphthalene). Copper salts were chosen based on oxidation state, reported use in literature, and availability; in addition, cleaned copper metal and copper oxide were also evaluated.[3a] The results of the experiments are shown in **Table 2-2**.

Table 2-2 Comparison of Copper Substrate and Binaphthalene Yield

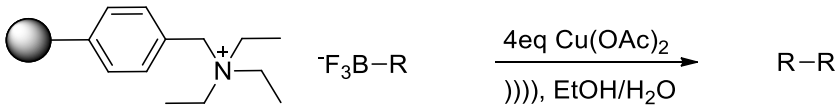
Copper Salt	% Yield Binaphthalene
$Cu(OAc)_2$	97
$CuSO_4$	3
CuI	7
Cu(0) metal	5
$CuNO_2$	53
Cu_2O	4
$CuCl_2$	17
CuCN	8

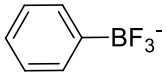
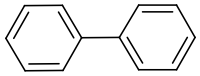
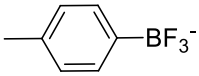
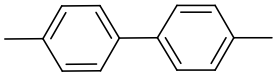
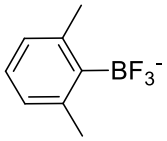
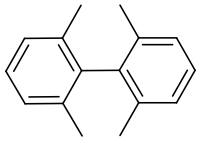
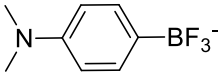
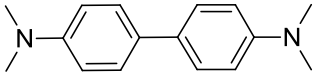
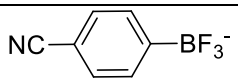
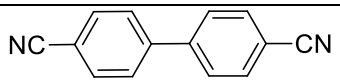
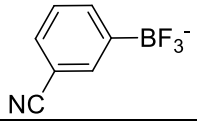
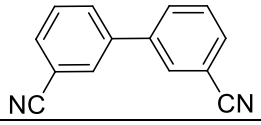
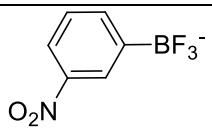
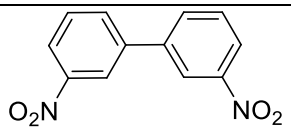
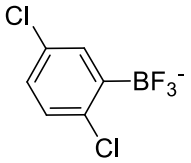
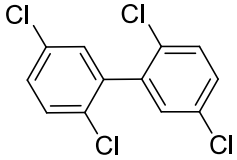
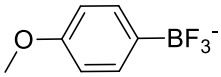
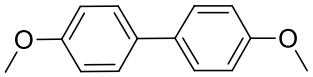
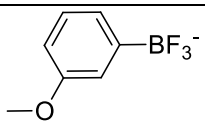
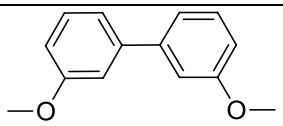
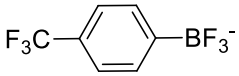
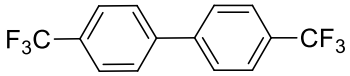
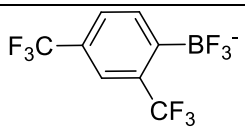
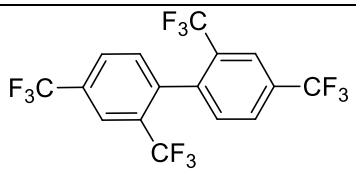
2.2.2 Homocoupling of Various Dowex Supported Aryltrifluoroborates

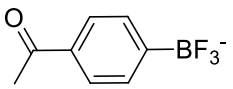
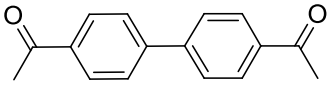
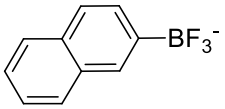
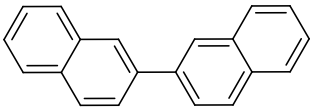
To evaluate the scope of the reaction noted in Scheme 2-3, a series of Dowex supported aryltrifluoroborates were synthesized (using the method developed by the Kabalka group), and subjected to the reported conditions.[25] The aryl substituents were

chosen with various electron donating or withdrawing groups, and with and without steric hindrance. The results of the reactions are listed in **Table 2-3**; the table lists the starting material and the product. All experiments were run in triplicate with the reported yields being the average of the reaction results.

Table 2-3 Homocoupling of Dowex-Supported Aryl Trifluoroborates

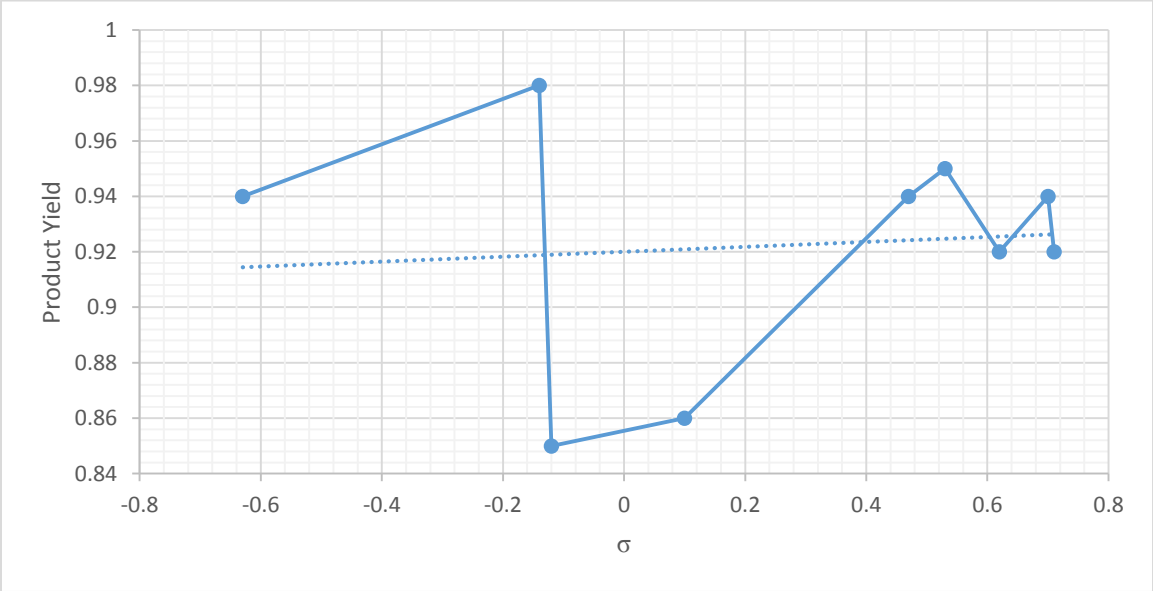


Entry	Starting Material	Product	Yield	Product Number
1			96%	201
2			98%	202
3			No reaction	203
4			94%	204
5			94%	205
6			92%	206
7			92%	207
8			56%	208
9			85%	209
10			86%	210
11			95%	211
12			No reaction	212

13			94%	213
14			97%	214

With the exception of the attempted synthesis of 2,2',6,6'-tetramethyl-1,1'-biphenyl and 2,2',4,4'-tetrakis(trifluoromethyl)-1,1'-biphenyl, the expected product was formed. It was determined that any unreacted aryltrifluorborate had hydrolyzed to an arylboronic acid.[31] In an attempt to evaluate the electronic effects of the substituent groups on the reaction, the yields were plotted against the reported sigma values, **Figure 2-1**:

Figure 2-1, Aryl Homocoupling Product Yields verse σ Values for Substituted Groups



Unfortunately, the pseudo Hammett plot does not provide useful information on the impact of the substituents on the reaction yields. The results of the reactions show improvement over reported yields from other homocoupling experiments that used an ultrasound source and previously reported yields from Ullmann or Suzuki experiments that were accomplished using traditional heating (with the exception of aryl groups that were sterically hindered).[2b, 13-14, 23b, 29b] It is hypothesized that the improved yields are a result of direct sonication of the reaction mixture. Survey experiments had been initially conducted using a bath sonicator; the results from these experiments were comparable to literature yields, and averaged 10-20% less product than those reported in Table 2-3.

The synthesis of compound 214 was repeated using a tenfold increase in the amount of all reagents and solvent. Sonication energy was increased to 20% amplitude (110 watts), and the reaction vessel was changed to a 100ml beaker. A final yield of 87% was determined, indicating that the aryl homocoupling reaction may be scalable.

2.2.3 Relationship to the Suzuki, Ullmann, and Chan-Evans-Lam Reactions

Examination of the reaction in Scheme 2-3 shows that it has properties of both the Ullmann and Suzuki cross-coupling reactions. The new method, Scheme 2-3, requires four equivalents of copper(II) acetate. Although the Ullmann reaction requires ten equivalents copper metal, it has been documented that if ultrasound is used as the energy source, only four equivalents of copper metal are required.[3a, 10, 13b] The Ullmann reaction typically requires 1-3 days of reaction time; the use of ultrasound decreases the reaction time to 2-8 hours.[3a, 10, 13b] There are differences between the developed method and the Ullmann reaction: the Ullmann reaction employs copper metal, copper oxide, and

copper(I) salts, but these materials showed no reactivity in the new method (see Table 2-1).

There are some similarities between the new method and the Suzuki coupling reaction: the reaction proceeds without the need for harsh conditions, an organoboron entity participates in the reaction, and the results of using ultrasound, instead of traditional heating, are in line with previous reports (shorter reaction times with improved yields).[5a] However, there is a significant difference: instead of using a palladium metal, copper(II) acetate is utilized as the reaction metal.

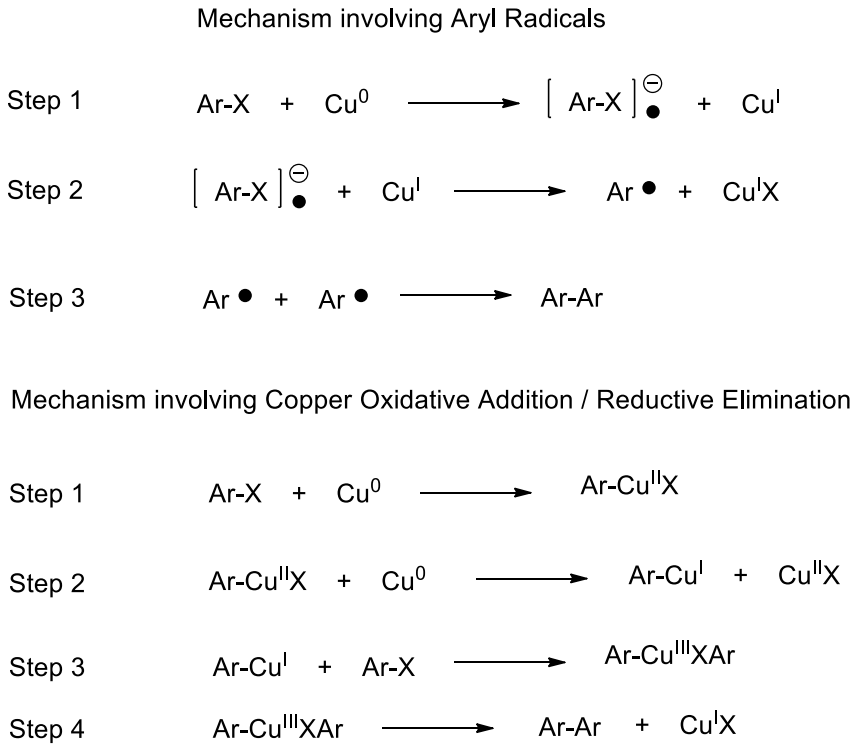
The new method most closely resembles the Chan-Evans-Lam modified Ullmann reaction. Copper(II) acetate and an arylborate are used in both reactions. There are three differences in the reactions: the Chan-Evans-Lam reaction has only been reportedly for coupling of an aryl carbon to a heteroatom (homocoupling has not been reported), the reaction proceeds at room temperature (ultrasound had not been applied to the earlier reactions), and no water can be present in the Chan-Evans-Lam reaction. The final difference between the two reactions is the requirement for an amine base. The new method uses a Dowex polymer that has a quaternary amine group. Since the reactants are exposed to high heat via ultrasound it is possible that this quaternary amine undergoes a Hofmann elimination resulting in a triethylamine base being produced.[1]

2.2.4 Mechanistic Study

The Ullmann coupling reaction was discovered in 1901, yet the exact mechanism is still not known.[1] Depending on the aryl species involved, and the reaction conditions used while conducting the Ullmann, it is hypothesized that the reaction can follow one of

two pathways: the first involves a single electron transfer from the copper metal to form an aryl radical, and the second involves an oxidation addition / reductive elimination of the copper metal (**Scheme 2-4**):[1, 21, 32]

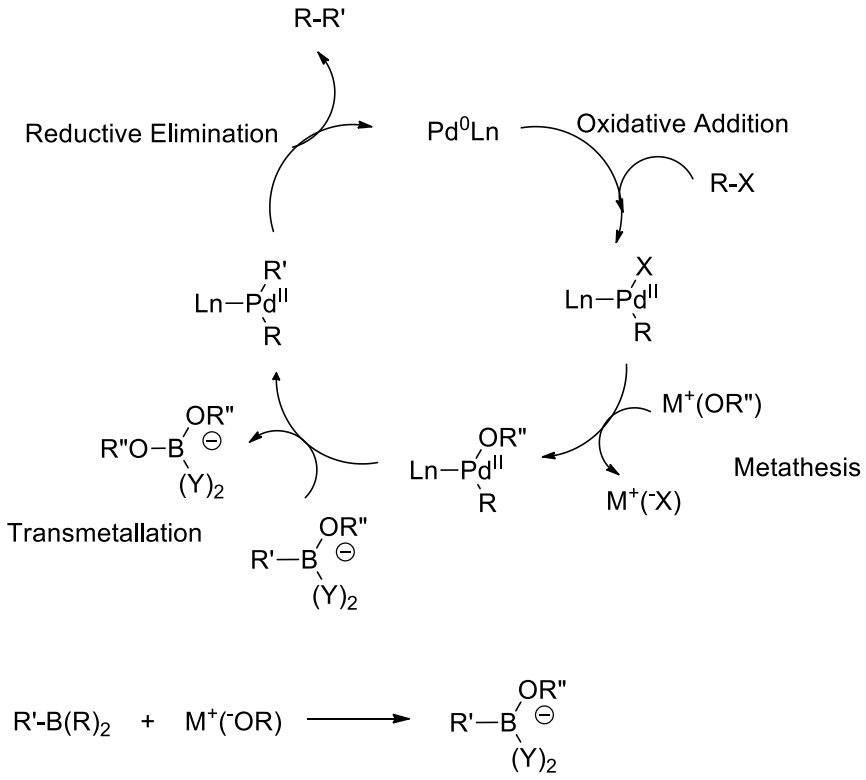
Scheme 2-4 Possible Ullmann Coupling Reaction Mechanism Pathways[1, 21, 32]



Studies conducted on the Chan-Evans-Lam reaction (although not carbon-carbon coupling related) indicate that the mechanism does not involve single electron transfer or free radicals.[6b] Using EPR copper(III) intermediates and a copper(I) product have been identified, providing significant evidence that it follows a pathway similar to the proposed oxidation addition / reduction elimination mechanism of the Ullmann (**Scheme 2-4**).[6b]

The Suzuki cross-coupling reaction is similar to many other reactions that involve a catalytic metal cycle, with four distinct steps: 1) the oxidative addition of an organic halide to the palladium metal, 2) metathesis, 3) transmetallation between palladium and an organoborate, and 4) reductive elimination to form a C-C bond and regeneration of the palladium metal (**Scheme 2-5**)

Scheme 2-5 Suzuki Cross-Coupling Mechanism



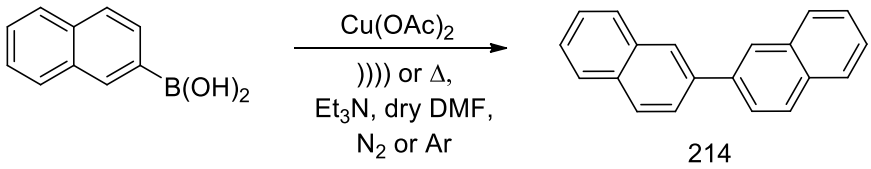
Using the published information on the three named reactions, a series of experiments were conducted to garner information related to the newly developed reaction's mechanistic pathway. It can be hypothesized that the reaction commences by

one of two routes: free-radical or oxidative addition / reductive elimination. In both mechanisms, it is projected that the copper(II) acetate would be converted to copper(I) acetate, which is water and air reactive.[33] To preserve this species for analysis, the reaction cannot be run in the aqueous ethanol and under air, but rather a dry system must be employed. For solubility reasons, an aryltrifluoroborate requires water to participate in a coupling reaction, this species would need to be changed to a system compatible with arylboronic acids.[31] To verify that the aryltrifluoroborates generate similar precursors to an arylboronic acid, ^{11}B NMR and an ESI Mass Spectrometry analysis were performed on post-reaction samples from a water based reaction and an anhydrous system. The primary boron species noted by NMR analysis were peaks at 19 ppm, corresponding to boric acid, and 32 ppm corresponding to naphthaboronic acid. There was an absence of a peak at 5 ppm corresponding to napthatrifluoroborate. ESI mass spectral analysis indicated that the unreacted aryl species was naphthaboronic acid and not naphthatrifluoroborate. The mass spectral and NMR evidence support the theory that the naphthatrifluoroborate generates intermediates similar to those generated by naphthaboronic acid precursors.[31] With this evidence it was decide to move ahead with additional reactions using arylboronic acids, in a dry system, to investigate the mechanism.

A series of experiments were set up using an anhydrous system under argon or dry nitrogen. Reactions were completed using both the ultrasound protocol and the traditional heating method (150 °C for 72 hours, and an increase to ten equivalents of copper(II) acetate).[10, 13b] The first set of reactions used only naphthaboronic acid and

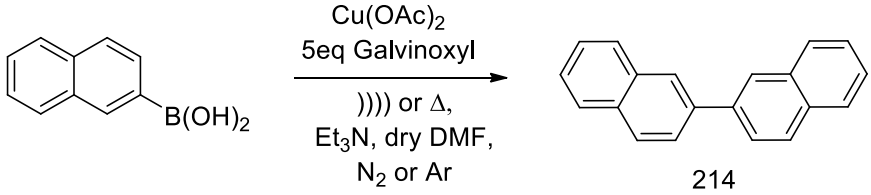
copper, there was no reaction, indicating that the Dowex polymer could be decomposing to an amine base.[1] To account for this aspect all other reactions were carried out using an equivalent of triethylamine (**Scheme 2-6**).

Scheme 2-6 Investigation of Mechanism



To determine if the reaction involves a free radical entity or single electron transfer, a similar set of reactions were run using the free-radical galvinoxyl (Aldrich G30-7) (**Scheme 2-7**). Using this compound, it is expected that any radical present would be immediately quenched, causing the reaction to terminate.

Scheme 2-7 Reaction for Investigation of Free Radical Mechanism



The reactions were run in triplicate, with the results shown in **Table 2-4** for compound 214.

Table 2-4 Product Yield Results for Mechanism Study, Compound 214

Entry	Reaction Conditions	Product Yield
1	Naphthaboronic acid, heat	0
2	Naphthaboronc acid, ultrasound	0
3	Naphthaboronic acid, heat, Et_3N	57
4	Naphthaboronic acid, ultrasound, Et_3N	53
5	Naphthaboronic acid, heat, Et_3N, galvinoxyl	56
6	Naphthaboronic acid, ultrasound, Et_3N, galvinoxyl	55

Post reaction, the copper residue was extracted under dry nitrogen, sealed in paraffin powder, and analyzed by scanning powder x-ray diffractometry.[33] The resulting spectra were compared to starting material copper(II) acetate and a purchased copper(I) acetate (Acros A0306322). Powder-XRD is not a standard method of analysis for different oxidation states, however it can be applied for detection in this case. The structure of copper(I) acetate is a polymeric planar chain, each copper atom being in a distorted square-planar environment, bonded to three oxygen atoms and another copper atom. The copper(II) acetate exists as a "paddlewheel" formation, the copper(II) ions are bridged in pairs by four acetate groups and two water molecules.[33-34] As the two different oxidation states have unit cell arrangements, the corresponding repeating unit will pack differently while forming a crystal. These different crystal configurations will give different 2θ values during pXRD analysis.[35] The results are shown in **Figures 2-2** through **2-7**.

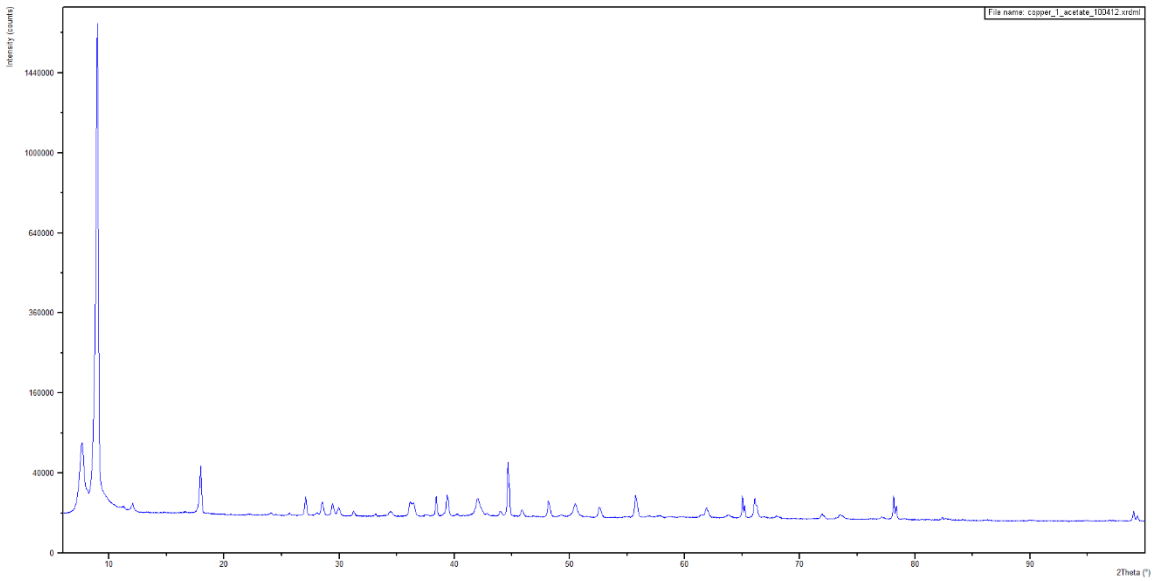


Figure 2-2 pXRD Spectrum of Copper(I) Acetate

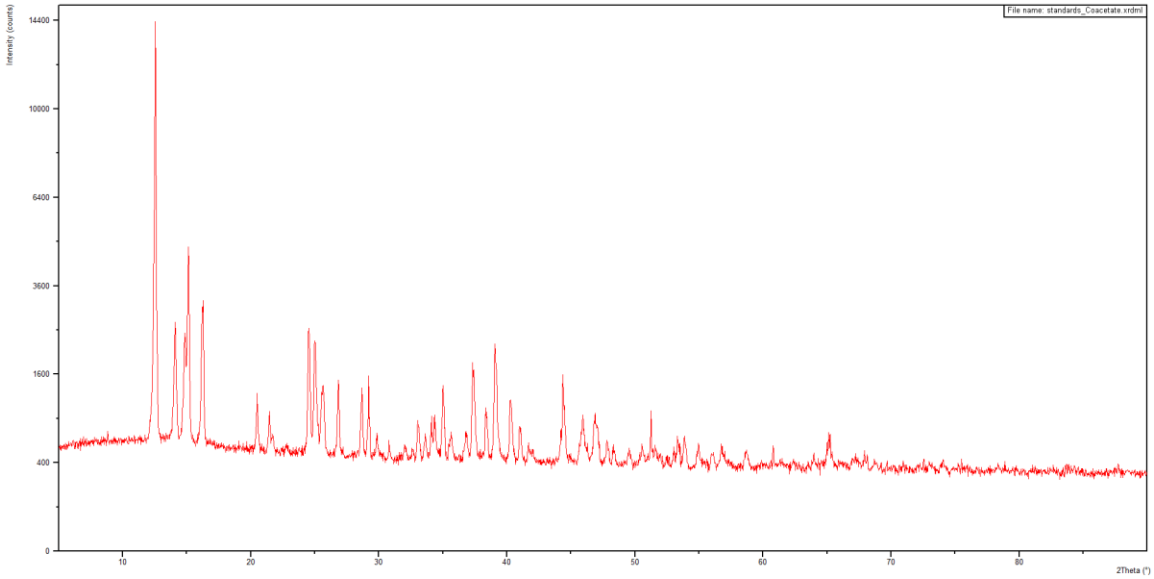


Figure 2-3 pXRD Spectrum of Copper(II) Acetate, Starting Material

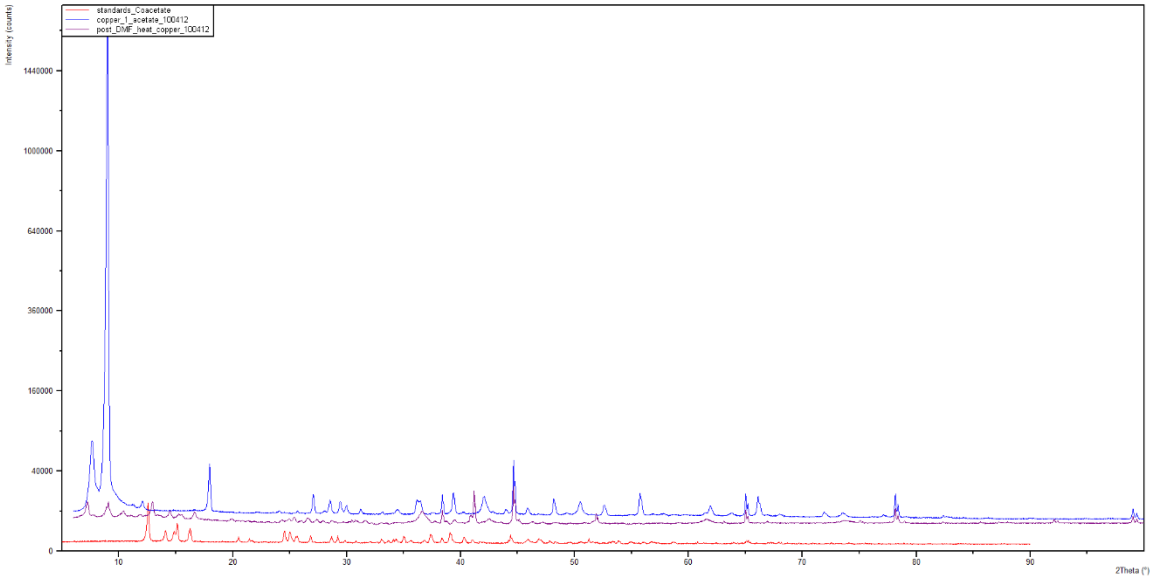


Figure 2-4 pXRD Spectrum of Extracted Copper from Entry 3, Table 2-4, Compared to Copper(I) and Copper(II) Standards

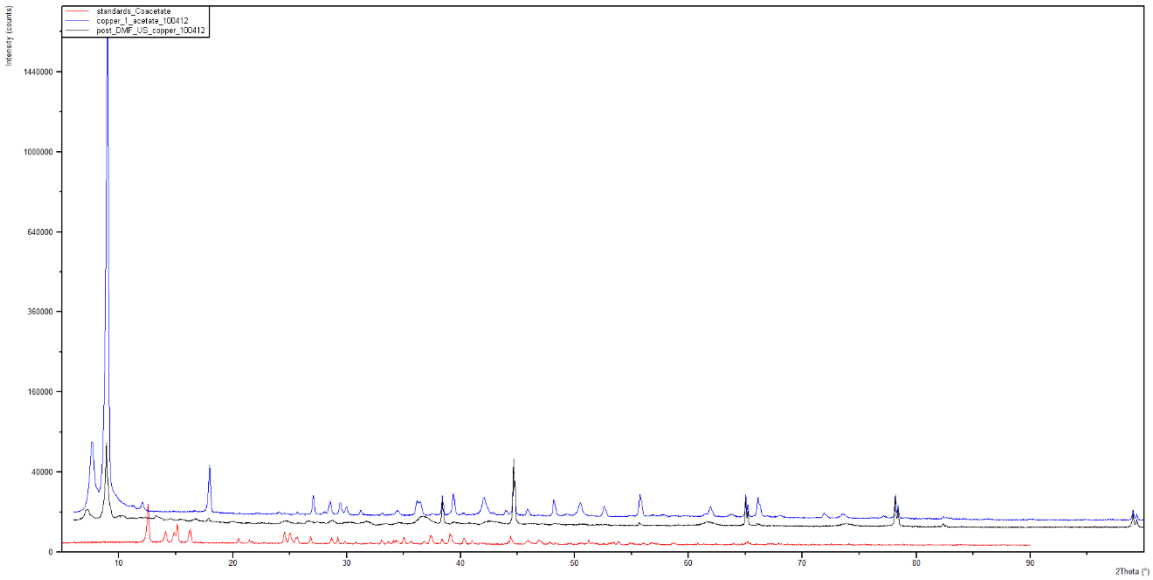


Figure 2-5 pXRD Spectrum of Extracted Copper from Entry 4, table 2-4, Compared to Copper(I) and Copper(II) Standards

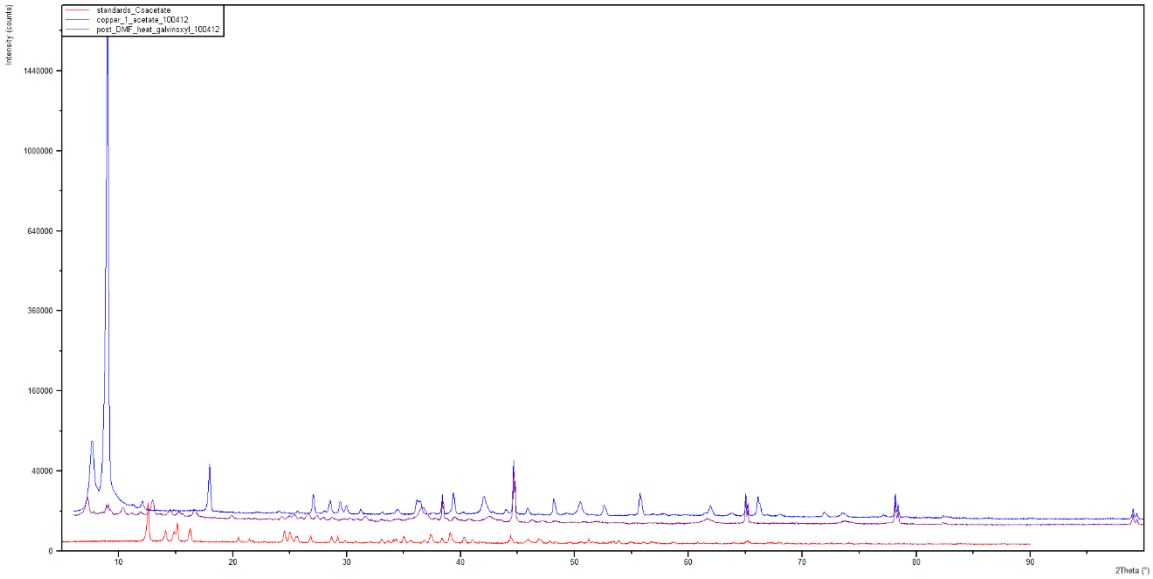


Figure 2-6 pXRD Spectrum of Extracted Copper from Entry 5, Table 2-4, Compared to Copper(I) and Copper(II) Standards

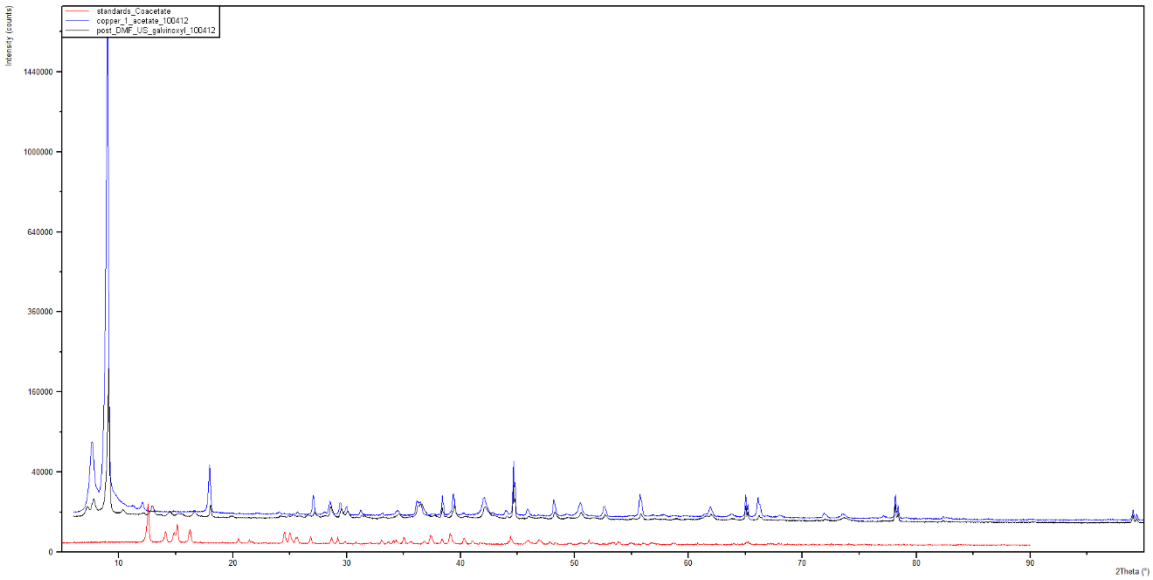


Figure 2-7 pXRD Spectrum of Extracted Copper from Entry 6, Table 2-4, Compared to Copper(I) and Copper(II) Standards

The product yields indicate that the galvinoxyl has no effect on the reaction, and pXRD analysis shows a strong indication that copper(I) acetate is produced in all reactions. The presence of the copper(I) acetate would explain the consumption of the copper during the reaction; since it is water reactive, it would immediately be converted to a hydrate. The evidence provides support for a mechanism that follows a pathway similar to that of the Ullmann reaction: oxidation addition / reductive elimination.

2.3 Conclusion

The homocoupling results collected in Table 2-3 indicate that the new ultrasound method has broad applicability with good product yields. The use of a Dowex polymer supported aryltrifluoroborate allows the reaction to be carried out in aqueous ethanol instead of an organic solvent, providing a "green" synthesis method. Using ultrasound as the energy source results in a dramatically shortened reaction times and decreases the quantity of metal catalyst required, while improving product yields. The reaction proceeds using copper(II) acetate instead of palladium metal, or other transition metals, allowing a cost effective, and safe means for the synthesis of biaryl compounds. The work presented in this chapter has been published:

"Ultrasound induced, copper mediated homocoupling using polymer supported aryltrifluoroborates," Musolino, B.; Quinn, M.; Hall, K.; Coltuclu, V.; Kabalka, G. W., *Tetrahedron Letters*, **2013**, 54(31), 4080-4082 .

2.4 Experimental Details

2.4.1 General Considerations

All glassware was dried at 120 °C and flushed with dry nitrogen prior to use. All chemicals were purchased from commercial sources and used as received. Dowex 1-X 10 (Bio.Rad Laboratories, 100-200 mesh, chloride form. Control number, MM06170). DI water (Barnstead E-pure) was used in all solution preparation and reactions. Potassium organotrifluoroborates were obtained from commercial sources or prepared from organoboronic acids according to reported procedures.[36] Gas Chromatography-Mass Spectroscopy studies were run on a Hewlett Packard: HP 6890 series GC System with 5973 Mass Selective Detector; Column: HP-5 30 m x 0.25 mm x 0.25 μm; Gas (He) flow 0.8 ml/min; temperature program: flow 0.8 ml/min, initial temperature 90 °C for 1 minute, a temperature ramp of 15 °/minute up to 200 °C, then a temperature ramp of 5 °/min to 250 °C for 10 minutes. All samples were purified using column chromatography (anhydrous sodium sulfate and 60 Å 230-400 mesh silica gel) and then recrystallized. All sonication experiments were carried out using a Fisher Scientific Model 550 Sonic Dismemborator, employing a 0.5 inch horn sonicator and a 1 inch by 2 inch cylindrical reaction vessel. All individual reactions were carried out in new borsite glass vessels.

2.4.2 Preparation of Dowex-Aryltrifluoroborate Complexes

All Dowex-aryltrifluoroborates were prepared by established procedures as reported by Kabalka et al.[25] A representative procedure for the synthesis of Dowex-napthatrifluoroborate: Dowex 1-X 10 (10 grams) was washed sequentially with 1 *N*

aqueous HCl (3 x 40 mL), 1 *N* aqueous NaOH (3 x 40 mL), water (100 mL) of water and then dried overnight prior to us. To a suspension of the base form of the Dowex resin (1 g) in H_2O (10 mL), a solution of 2-naphthylenyltrifluoroborate (1 mmol) in MeOH (10 mL) was added in one portion. The pH of the reaction mixture was then monitored to determine reaction termination.

2.4.3 Representative Procedure for the Synthesis of Binaphthalene

Naphthyltrifluoroborate-Dowex resin (1.25 g, equivalent to 0.5 mmol of naphthyltrifluoroborate) was added to 15 milliliters of 1:1 water / EtOH solvent; 2.0 mmol of copper(II) acetate was added, and the dismemberator horn placed in the reaction vessel. The sonicator was set to 55 watts and the reaction was allowed to proceed for 6 hours (1 minute pulse with a 3 second rest). Post reaction, the mixture was extracted with dichloromethane for subsequent purification and analytical analysis.

Yields of the 2,2'-binaphthalene were determined by a calibrated gas chromatograph / mass spectrometer, using a purchased 2-2'-binaphthalene standard (Aldrich S413402), the curve was seven points, with an R^2 of 0.9998, and with random samples verified by weight. All other synthesized biaryls yields were determined by weight.

2.4.4 Characterization of Compounds 201-214

^{1}H NMR and ^{13}C NMR spectra were recorded either at 250 and 63 MHz or 300 and 75 MHz respectively. Chemical shifts for ^{1}HNMR and ^{13}CNMR spectra were referenced to TMS and the d-chloroform solvent shift. High quality mass spectrometry was carried out using a Qstar electron spray ionization mass spectrometer, in either

positive (M+1) or negative mode (M-1), ionization energy of ±5000 e/v, injection rate of 20 μl/min.

1,1'-Biphenyl (201)[29b]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.46 (dt, *J* = 34.1, 7.4 Hz, 10H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 145.1, 127.9, 125.9, 125.8. Anal. Calcd for $C_{12}H_{10}$: 154.0783. Found: 155.08111 (M+1). GC RT: 4.01 minutes.

4,4'-Dimethyl-1,1'-biphenyl (202)[29b]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.36 – 7.15 (m, 4H), 3.66 (s, 6H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 136.6, 129.5, 127.8, 126.8, 126.5. Anal. Calcd for $C_{14}H_{14}$: 182.1096. Found: 183.0988 (M+1). GC RT: 6.11 minutes.

N4,N4,N4',N4'-Tetramethyl-[1,1'-biphenyl]-4,4'-diamine (204)[37]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 9.0 Hz, 4H), 6.70 (d, *J* = 9.0 Hz, 4H), 3.09 (s, 12H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 154.2, 133.5, 129.5, 110.5, 39.8, Anal. Calcd for $C_{16}H_{20}N_2$: 240.1626. Found: 241.1771 (M+1). GC RT: 12.02 minutes.

[1,1'-Biphenyl]-4,4'-dicarbonitrile (205)[37]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 7.9 Hz, 4H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 142.6, 134.3, 127.8, 118.2, 112.9. Anal. Calcd for $C_{14}H_8N_2$: 204.0687. Found: 205.0721 (M+1). GC RT: 5.03 minutes.

[1,1'-Biphenyl]-3,3'-dicarbonitrile (206):[38] ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.85 (s, 2H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.6 Hz, 2H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 142.6, 132.1, 130.1, 129.5, 117.3, 112.9. Anal. Calcd for $C_{14}H_8N_2$: 204.0687. Found: 205.0714 (M+1). GC RT: 6.83 minutes.

3,3'-Dinitro-1,1'-biphenyl (207)[37]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.95 (ddd, *J* = 8.0, 1.7, 1.1 Hz, 4H), 7.71 – 7.61 (m, 4H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 148.1, 139.7,

136.6, 129.5, 126.8, 126.5. Anal. Calcd for $C_{12}H_8N_2O_4$: Exact Mass: 244.0484. Found: 243.0555 (M-1). GC RT: 7.81 minutes.

2,2',5,5'-Tetrachloro-1,1'-biphenyl (208)[39]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.89 (s, 2H), 7.61 (dd, *J* = 8.6, 2.5 Hz, 4H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 137.8, 134.0, 130.8, 129.6, 125.4. Anal. Calcd for $C_{12}H_6Cl_4$: 289.9224. Found: 289.0012 (M-1). GC RT: 8.76 minutes.

4,4'-Dimethoxy-1,1'-biphenyl (209)[29b]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 3.4 Hz, 4H), 7.15 (d, *J* = 7.7 Hz, 4H), 3.74 (s, 6H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 162.2, 133.6, 129.1, 114.3, 53.7. Anal. Calcd for $C_{14}H_{14}O_2$: 214.0994. Found: 215.1001 (M+1). GC RT: 6.46 minutes.

3,3'-Dimethoxy-1,1'-biphenyl (210)[37]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.95 (s, 2H), 7.36 – 7.24 (m, 4H), 6.90 (t, *J* = 1.0 Hz, 2H), 3.82 (s, 6H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 162.2, 147.2, 128.8, 121.1, 112.4, 55.6. Anal. Calcd for $C_{14}H_{14}O_2$: 214.0994. Found: 215.1103 (M+1). GC RT: 6.33 minutes.

4,4'-Bis(trifluoromethyl)-1,1'-biphenyl (211)[40]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.81 (dd, *J* = 23.5, 8.8 Hz, 4H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 147.7, 133.9, 131.6, 126.2, 124.8. Anal. Calcd for $C_{14}H_8F_6$: 290.0530. Found: 289.0666 (M-1). GC RT: 8.25 minutes.

1,1'-([1,1'-Biphenyl]-4,4'-diyl)diethanone (213)[40]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 8.3 Hz, 4H), 7.59 (d, *J* = 8.5 Hz, 4H), 2.49 (s, 6H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 192.9, 146.5, 136.6, 127.9, 125.8, 26.4 Anal. Calcd for $C_{16}H_{14}O_2$: 238.0994. Found: 237.1142 (M-1). GC RT: 6.77 minutes.

2,2'-Binaphthalene (214)[29b]: ^{1}HNMR (250 MHz, Deuterium Oxide) δ 7.84 (dd, *J* = 6.2, 3.3 Hz, 6H), 7.57 (s, 2H), 7.47 (dd, *J* = 6.2, 3.3 Hz, 6H). ^{13}CNMR (63 MHz, D_2O) δ 138.4, 133.7, 132.7, 128.5, 128.2, 127.7, 126.3, 126.1, 126.0, 125.7. Anal. Calcd for $C_{20}H_{14}$: 254.1096 Found: 255.1105 (M+1). GC RT 9.53 minutes.

CHAPTER III
COUPLING OF ARYLBORATES TO PHENOLS: APPLICATION OF ULTRASOUND TO THE CHAN-EVANS-LAM REACTION

3.1 Introduction

O-arylation reaction is a key synthetic route to diaryl ethers used as starting materials in organic and bio-chemistry. In 1903, the Ullmann reaction was expanded to include the coupling of aryl halides and phenols, providing chemists an effective means for this synthesis.[2a] The harsh conditions and less than desirable yields of the Ullmann reaction, motivated chemists to devise a new pathway for diaryl ether synthesis. Unfortunately, many of the developed reactions were limited in scope or did not improve upon the conditions of the Ullmann reaction.[2a] From 1998 through 2001, the Chan-Evans-Lam modified Ullmann reaction was continually developed.[3b-d] Initially it was established for C-N coupling but it was soon found that the reaction could be used to couple aryl carbon to other heteroatoms, including oxygen.[6b] The reaction is conducted under mild conditions, at room temperature, and under atmospheric conditions (Scheme 1-8); however, water poisons the reaction, the reaction time is typically 1-3 days, and the product yields are equivalent to those of the Ullmann reaction.[2a, 6b, 7c]

With the success of the aryl homocoupling reactions described in Chapter 2 and the apparent relationship between that method and the Chan-Evans-Lam reaction, it was decided to apply ultrasound to the Chan-Evans-Lam reaction. To our knowledge, the direct application of ultrasound to the O-arylation of phenols, under the conditions of the Chan-Evans-Lam reaction, has not been reported.

3.2 Results and Discussion

To determine the feasibility of ultrasound to the Chan-Evans-Lam reaction, a series of survey experiments were conducted using phenol:

Reaction with Dowex-naphthyltrifluoroborate in aqueous ethanol: employing the method outlined in Scheme 2-3, Dowex support naphthyltrifluoroborate (0.5 mmol) was mixed with an equal equivalence of phenol (0.5 mmol), 4 equivalents of copper(II) acetate, in aqueous ethanol, and exposed to ultrasound irradiation for 6 hours. A control experiments using the same reaction mixture was stirred at room temperature for 72 hours without ultrasound activation. No product was formed in either reaction.

Reaction with Dowex-naphthyltrifluoroborate in DCM: employing the method outlined in Scheme 2-3, Dowex support naphthyltrifluoroborate was mixed with an equal equivalence of phenol, 4 equivalents of copper(II) acetate but dichloromethane was used as the solvent and the reaction mixture was exposed to ultrasound irradiation for the 6 hours. Since the heat generated by the ultrasound is high enough to evaporate the DCM, the reaction vessel was placed in an ice/water bath; the external reaction vessel was maintained at 0-5 °C. A control experiment was carried out using the same reaction mixture while stirring at room temperature for 72 hours. No product was formed in either reaction, supporting by Molander's observation that water must be present for a trifluoroborate to react.[31]

Reaction with Naphthaboronic Acid and Triethylamine in DCM: 1 equivalent of phenol and 1.5 equivalent of naphthaboronic acid were mixed in DCM, along with 5.0 equivalents of triethylamine base, and 4 equivalents of copper(II) acetate, and then the

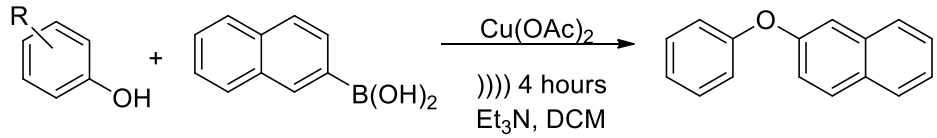
mixture was exposed to ultrasound irradiation for 6 hours. The increased equivalents of naphthaboronic acid was used to account for the presence of trimeric cyclic anhydrides. Since the heat generated by the ultrasound is high enough to evaporate the DCM, the reaction vessel was placed in an ice/water bath; the external reaction vessel was maintained at 0-5 °C. A control experiment was carried out using the same reaction mixture while stirring at room temperature for 6 and 72 hours. The ultrasound experiment gave a product yield of 94%, the 6 hour control a yield of 23%, and the 72 hour control a yield of 72%. The ultrasound experiment was repeated, but the reaction time was reduced to 4 hours, and the amount of copper(II) acetate was decreased from 4 equivalents to 1 equivalent. The product yield was found to be 92%. It is possible that the cooling of the ice bath has a beneficial affect on the reaction: with a cooler solvent system the ultrasound probe would be able to more easily shed built up internal heat, and thus improve the heat transfer from the probe to the surrounding media.[9]

The new method was evaluated employing various arylborates and phenols. Arylborates and phenols were chosen to include electron donating groups, electron withdrawing groups, and sterically hindered groups.

3.2.1 Reaction of Naphthaboronic Acid with Phenols

Various phenols were mixed in DCM, with napthylboronic acid, copper(II) acetate, and triethylamine. The reaction results are shown in **Table 3-1**.

Table 3-1 Reaction Results for Naphthylboronic Acid and Phenols



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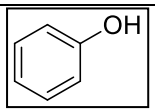
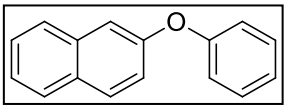
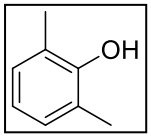
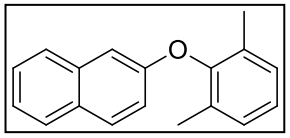
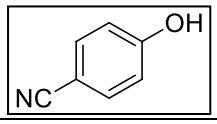
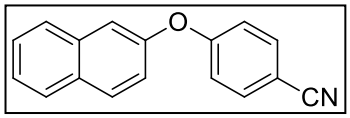
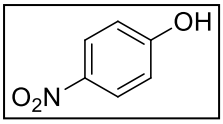
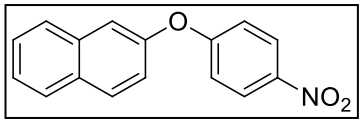
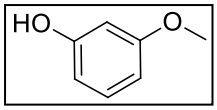
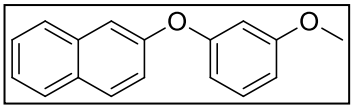
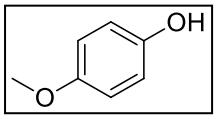
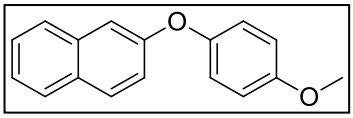
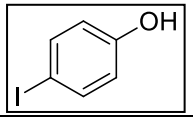
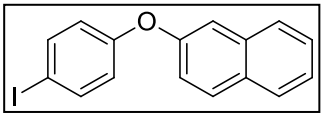
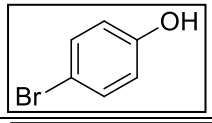
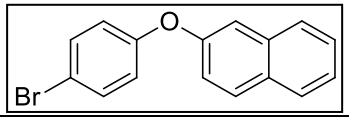
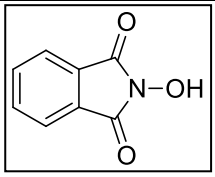
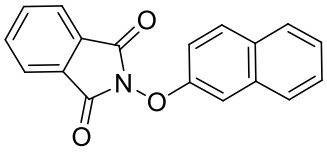
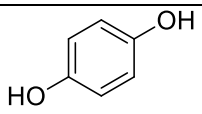
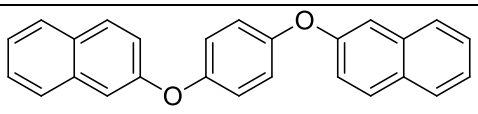
1			92	301
2			81	302
3			97	303
4			91	304
5			88	305
6			NR	306
7			93	307
8			92	308
9			53	309
10			NR	310

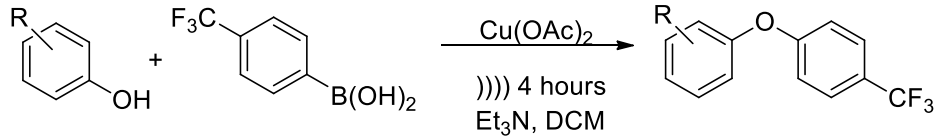
With the exception of the attempted synthesis of 2-(4-methoxyphenoxy)naphthalene and 1,4-bis(naphthalen-2-yloxy)benzene, the expected product was formed. There was no homocoupling product detected, and all unreacted naphthylboronic acid remained as the boronic acid.

The synthesis of compound 301 was repeated using a tenfold increase in the amount of all reagents and solvent. Sonication energy was increased to 20% amplitude (110 watts), and the reaction vessel was changed to a 100ml beaker. A final yield of 80% was obtained, indicating that the O-arylation reaction is scalable.

3.2.2 Reaction of (4-(Trifluoromethyl)phenyl)boronic Acid with Phenols

Various phenols were mixed in DCM, with (4-(trifluoromethyl)phenyl)boronic acid, copper(II) acetate, and triethylamine. The results are presented in **Table 3-2**.

Table 3-2 Results of the Reaction of Phenols with (4-(Trifluoromethyl)phenyl)boronic acid



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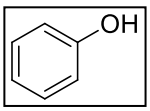
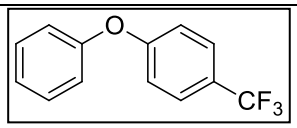
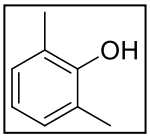
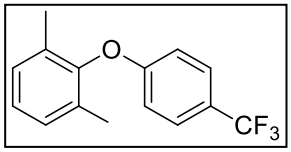
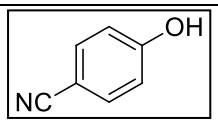
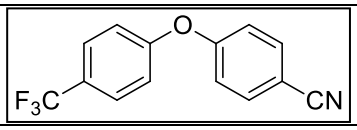
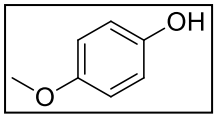
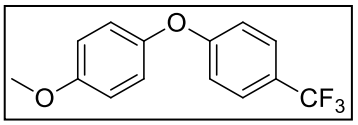
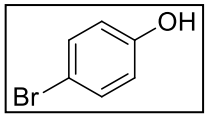
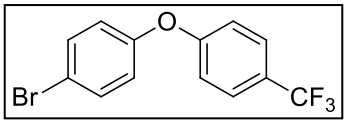
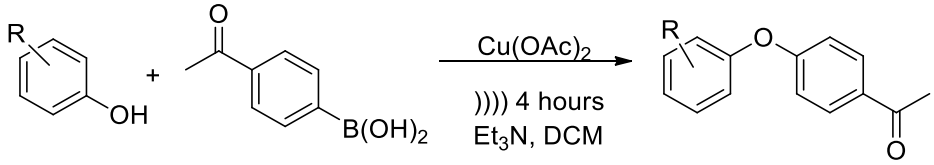
1			97	311
2			88	312
3			90	313
4			NR	314
5			97	315

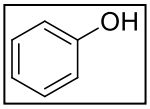
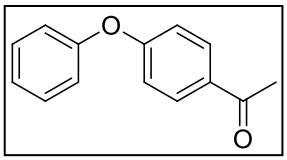
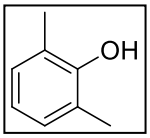
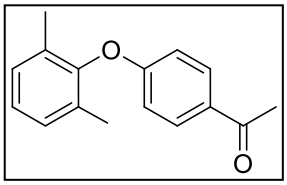
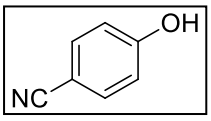
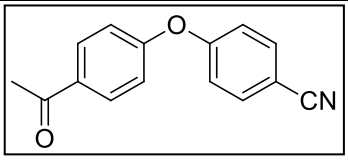
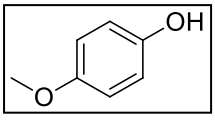
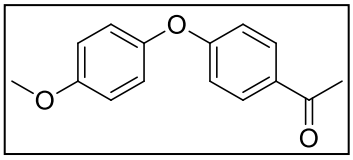
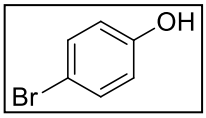
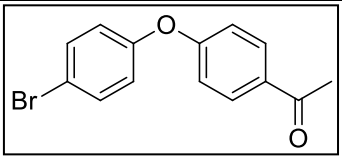
With the exception of the attempted synthesis of 1-methoxy-4-(4-(trifluoromethyl)phenoxy)benzene, the expected product was formed. There was no homocoupling product detected, and all unreacted naphthylboronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

3.2.3 Reaction of (4-Acetylphenyl)boronic Acid with Phenols

Various phenols were mixed in DCM, with (4-acetylphenyl)boronic acid, copper(II) acetate, and triethylamine. The results are presented in **Table 3-3**.

Table 3-3 Reaction Results of Phenols with (4-Acetylphenyl)boronic Acid



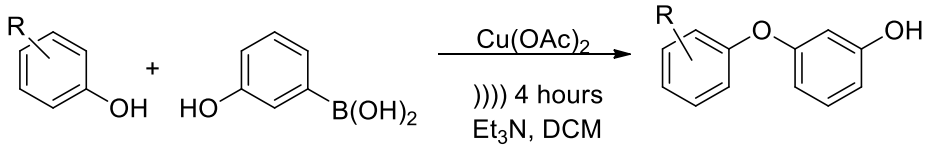
Entry	Starting Material	Product	Yield	Product
1			91	316
2			81	317
3			89	318
4			NR	319
5			88	320

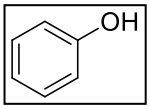
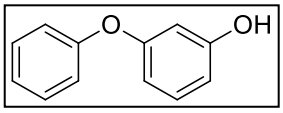
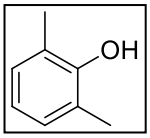
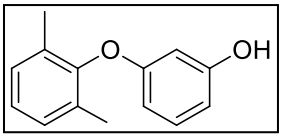
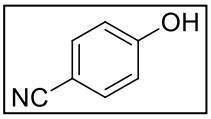
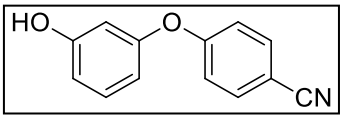
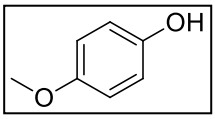
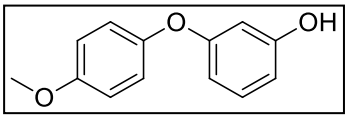
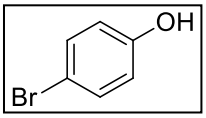
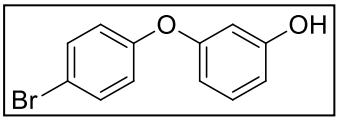
With the exception of the attempted synthesis of 1-(4-(4-methoxyphenoxy)phenyl)ethanone, the expected product was formed. There was no homocoupling product detected, and all unreacted naphthylboronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

3.2.4 Reaction of (3-Hydroxyphenyl)boronic Acid with Phenols

Various phenols were mixed in DCM, with (3-hydroxyphenyl)boronic acid, copper(II) acetate, and triethylamine. The results are presented in **Table 3-4**.

Table 3-4 Results of Reaction between Phenols and (3-Hydroxyphenyl)boronic Acid



Entry	Starting Material	Product	Yield	Product
1			76	321
2			72	322
3			66	323
4			NR	324
5			76	325

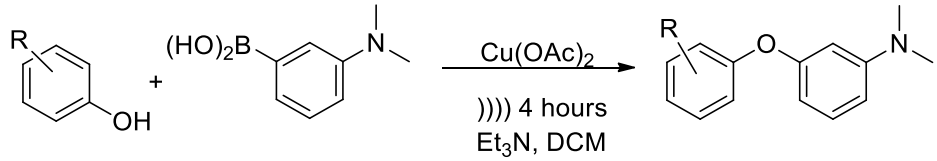
With the exception of the attempted synthesis of 3-(4-methoxyphenoxy)phenol, the expected product was formed. There was no homocoupling product detected, and all

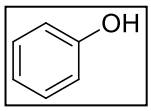
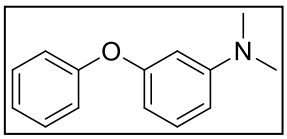
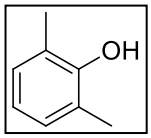
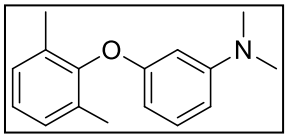
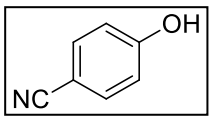
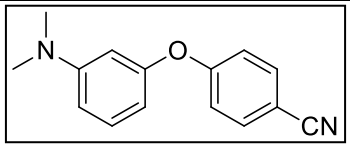
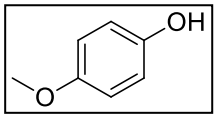
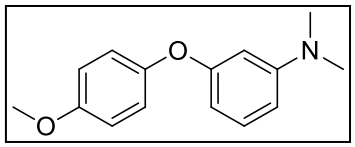
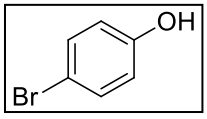
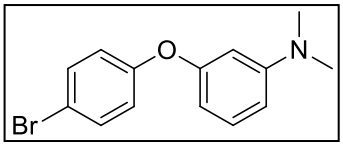
unreacted naphthylboronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

3.2.5 Reaction of (3-(Dimethylamine)phenyl)boronic Acid with Phenols

Various phenols were mixed in DCM, with (3-(dimethylamino)phenyl)boronic acid, copper(II) acetate, and triethylamine. The results are presented in **Table 3-5.**

Table 3-5 Results of Reaction between Phenols and (3-(Dimethylamino)phenyl)boronic Acid



Entry	Starting Material	Product	Yield	Product
1			72	326
2			NR	327
3			68	328
4			NR	329
5			NR	330

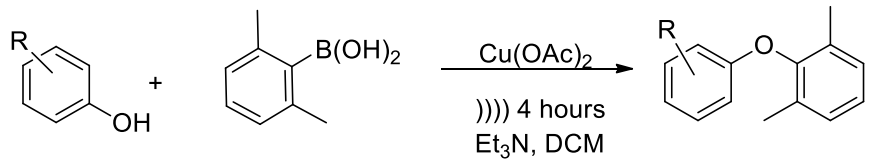
With the exception of the attempted synthesis of 3-(2,6-dimethylphenoxy)-N,N-dimethylaniline, 3-(4-methoxyphenoxy)-N,N-dimethylaniline, and 3-(4-bromophenoxy)-N,N-dimethylaniline, the expected product was formed. There was no homocoupling product detected, and all unreacted naphthylboronic acid remained as the boronic acid.

The reactions that showed no product yield had the results verified by additional experiments.

3.2.6 Reaction of (2,6-Dimethylphenyl)boronic Acid with Phenols

Various phenols were mixed in DCM, with (2,6-dimethylphenyl)boronic acid, copper(II) acetate, and triethylamine (**Scheme 3-1**). There was no product formed in these reaction. The results were verified by additional experiments, including one carried out using 6 hours of ultrasonic radiation.

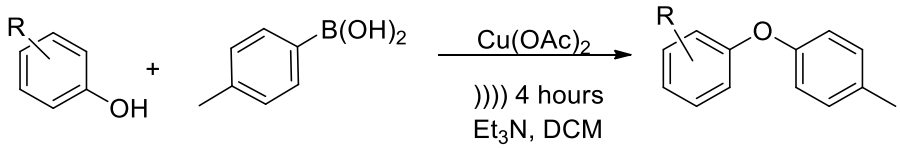
Scheme 3-1 Reaction of (2,6-Dimethylphenyl)boronic Acid with Phenols

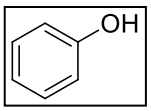
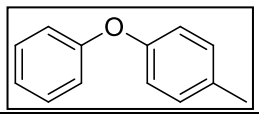
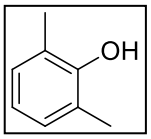
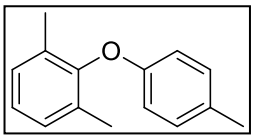
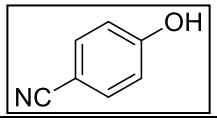
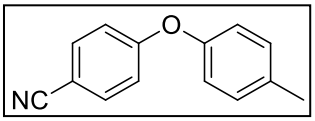
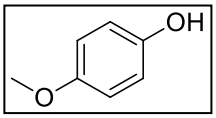
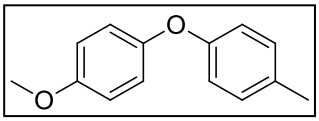
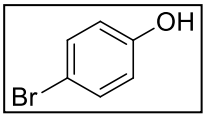
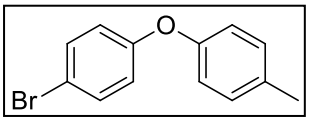


3.2.7 Reaction of P-Tolyboronic Acid with Phenols

Various phenols were mixed in DCM, p-tolylboronic acid, copper (II) acetate, and triethylamine. The results are presented in **Table 3-6**.

Table 3-6 Results of Reaction of Phenols with p-Tolylboronic Acid

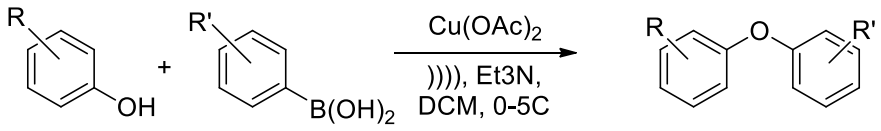


Entry	Starting Material	Product	Yield	Product
1			85	331
2			88	332
3			92	333
4			NR	334
5			93	335

With the exception of the attempted synthesis of 1-methoxy-4-(p-tolyloxy)benzene, the expected product was formed. There was no homocoupling product detected, all unreacted naphthylboronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

In an attempt to evaluate the electronic effects of the substituent groups on the reaction, the yields were plotted against the reported sigma values, **Table 3-7**:

Table 3-7 Plot of Reactant Sigma Values correlated with Product Yield



R ↓ R' →	meta -OH	meta -NMe2	para -CH3	para -C(O)CH3	para -CF3
para-OCH3	**0**	**0**	**0**	**0**	**0**
H	**76**	**72**	**85**	**91**	**97**
para -Br	**76**	**0**	**93**	**88**	**97**
para -CN	**66**	**68**	**92**	**89**	**90**
2,6 – CH3	**72**	**0**	**88**	**81**	**88**

The data indicates that the highest product yields occur when the boronic acid contains an electron withdrawing group, while the phenol has a sigma value close to zero.

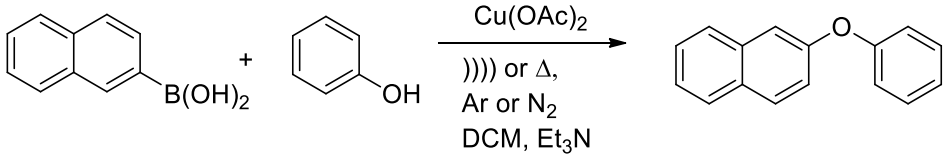
3.2.8 Mechanistic Study

The mechanism of the Chan-Evans-Lam copper-catalyzed oxidative O-arylation reactions has been extensively studied but is still not fully understood.[6b] A detailed mechanistic study was performed by King, Stahl, et al. that provided insight into the reaction pathway: EPR studies conducted during the reaction detected the presence of copper(III) intermediates and a copper(I) product, providing evidence that the reaction follows a similar pathway to the proposed oxidation addition / reduction elimination

mechanism of the Ullmann reaction (Scheme 2-4).[41] To determine if free-radicals participated in the reaction, Lam and coworkers carried out several experiments using the free-radical trap 1-diphenylethylene which had no effect on the reaction.[6b] However, these studies were conducted under thermal conditions that commence at room temperature, without the application of energy (e.g. ultrasound).[3d]

It is possible that ultrasound could generate free-radicals.[42] To insure that this generation is not occurring in our studies, a series of experiments were conducted; a summary is shown in **Table 3-8**. This series was designed to test for the presence of copper(I) acetate and free radicals. All experiments were conducted as described in Section 2.2.4.

Table 3-8 Summary of Mechanism Investigation Experiments



Entry	Reaction Conditions	Product Yield
1	Naphthylboronic acid, phenol, R.T., 72 hours	72
2	Naphthylboronic acid, phenol, ultrasound 4 hours	92
3	Naphthylboronic acid, phenol, 5eq galvinoxyl R.T., 72 hours	69
4	Naphthylboronic acid, phenol, 5eq galvinoxyl ultrasound 4 hours	90

It is not possible to conduct an ultrasound experiment in the presence of EPR, so to determine if copper(I) acetate was produced, scanning powder-x-ray diffraction was employed. The pXRD analysis showed that all samples showed two theta peaks associated with copper(I) acetate (2θ: 4.3, 7.2, 18, 26.7, 37, 42, 44.8; as compared to the copper(I) standard post reaction. The added galvinoxyl had no impact on the reaction

product yield. This evidence supports the postulation that ultrasound has no effect on the reaction mechanism.

3.3 Conclusion

The application of ultrasound to the Chan-Lam-Evans modified Ullmann reaction has shown great benefit for the generation of biaryl ethers. Although the original reaction does not call for the addition of energy, ultrasound dramatically decreased the reaction time from 72 hours to 4 hours while improving the product yields from the 30-80% range to a compound related range of 60-100%. The resulting yields seem to indicate an electronic effect related to the arylboronic acid, which may warrant additional study from further method development. Unfortunately the use of an aqueous solvent system and polymer support are not applicable. Lam et al. report that O-arylation does not occur in some isolated cases and attributes the lack of reaction to a possible amine base affect.[7c] With the exception of Section 3.2.6, experiments that did not produce any yields are similar to the unsuccessful reactions reported by Lam.

3.4 Experimental Details

3.4.1 General Considerations

All glassware was dried at 120 °C and flushed with dry nitrogen prior to use. All chemicals were purchased from commercial sources and used as received. Dowex 1-X 10 (Bio.Rad Laboratories, 100-200 mesh, chloride form. Control number, MM06170). DI water (Barnstead E-pure) was used in all solution preparation and reactions. Potassium organotrifluoroborates were obtained from commercial sources or prepared from organoboronic acids or esters according to the reported procedures.[36]

Gas Chromatography-Mass Spectroscopy studies were carried out on a Hewlett Packard: HP 6890 series GC System with 5973 Mass Selective Detector; Column: HP-5 30 m x 0.25 mm x 0.25 μm; Gas (He) flow 0.8 ml/min; temperature program: flow 0.8 ml/min, initial temperature 90 °C for 1 minute, a temperature ramp of 15 °/minute up to 200 °C, then a temperature ramp of 5 °/min up to 250 °C for 10 minutes. All samples were purified using column chromatography (anhydrous sodium sulfate and 60 Å 230-400 mesh silica gel), and then recrystallized.

All sonication experiments were carried out using a Fisher Scientific Model 550 Sonic Dismemborator, employing a 0.5 inch horn sonicator and a 1 inch by 2 inch cylindrical reaction vessel. All individual reactions were carried out in new borsite glass vessels. Reaction vessel external temperature was maintained at 0-5 °C with an ice water bath.

3.4.2 Preparation of Dowex-Napthyl-Trifluoroborate Complex

The Dowex-naphthyltrifluoroborate was prepared by the procedure developed by Kabalka et al:[25] Dowex 1-X 10 (10 grams) was washed sequentially with 1*N* aqueous HCl (3 x 40 mL), 1 *N* aqueous NaOH (3 x 40 mL), water (100 mL) of water and then dried overnight prior to us. To a suspension of the base form of the Dowex resin (1g) in H_2O (10 mL), a solution of 2-naphthylenyltrifluoroborate (1 mmol) in MeOH (10 mL) was added in one portion. The pH of the reaction mixture was then monitored to determine reaction termination.

3.4.3 Representative Procedure for the Synthesis of 2-phenoxynaphthalene

Naphthylboronic acid (0.25 g, 1.5 mmol) was added with 0.094 g of phenol (1 mmol) to 15 ml of DCM. Copper(II) acetate (0.36 g, 2.0 mmol) was then added along with triethylamine (0.5g, 5.0 mmol), and the dismemberator horn placed in the reaction vessel. The sonicator was set to 55 watts and the reaction was allowed to proceed for 4 hours (1 minute pulse with a 3 second rest). Post reaction, the product was isolated by column chromatography. Product yields were determined by weight and purity was confirmed by GC/MS and NMR.

3.4.4 Characterization of Compounds 301-334

^{1}H NMR and ^{13}C NMR spectra were recorded either at 250 and 63 MHz or 300 and 75 MHz respectively. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra were referenced to TMS and the d-chloroform solvent shift. High quality mass spectrometry was carried out using a Qstar electron spray ionization mass spectrometer, in either positive (M+1) or negative mode (M-1), ionization energy of ±5000 e/v, injection rate of 20 μl/min.

2-Phenoxynaphthalene (301)[43]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.93 (dt, *J* = 6.2, 3.1 Hz, 3H), 7.63 – 7.40 (m, 5H), 7.22 (dd, *J* = 17.6, 8.1 Hz, 4H). ^{13}CNMR (75 MHz, $cdcl_3$) δ 157.4, 151.4, 134.3, 130.6, 129.5, 127.8, 126.7, 126.4, 125.2, 123.0, 119.2, 116.9, 108.1. Anal. Calcd for $C_{16}H_{12}O$: 220.0888. Found: 221.1001 (M+1). GC RT 6.78 minutes.

2-(2,6-Dimethylphenoxy)naphthalene (302)[43]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.90 (dd, *J* = 6.2, 3.3 Hz, 5H), 7.53 (dd, *J* = 6.3, 3.3 Hz, 4H), 7.23 – 7.13 (m, 2H), 7.03

(d, *J* = 7.3 Hz, 2H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 154.6, 151.2, 133.3, 129.0, 128.5, 126.7, 126.3, 125.7, 125.1, 123.8, 123.2, 114.4, 108.0, 16.8. Anal. Calcd for $C_{18}H_{16}O$: 248.1201 Found: 249.1113 (M+1). GC RT 7.48 minutes.

4-(Naphthalen-2-yloxy)benzonitrile (303)[43]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 6.2, 3.3 Hz, 4H), 7.66 – 7.49 (m, 3H), 7.39 (s, 1H), 7.08 (d, *J* = 8.7 Hz, 3H). ^{13}CNMR (63 MHz, D_2O) δ 161.9, 153.9, 133.8, 132.9, 130.1, 129.2, 127.4, 125.4, 122.9, 119.5, 117.6, 116.5, 109.2, 104.6. Anal. Calcd for $C_{17}H_{11}NO$: 245.0841. Found: 244.0900 (M-1). GC RT 18.05 minutes.

2-(4-Nitrophenoxy)naphthalene (304)[44] ^{1}HNMR (300 MHz, Chloroform-*d*) δ 8.24 (d, *J* = 9.2 Hz, 1H), 7.87 (dd, *J* = 6.2, 3.3 Hz, 17H), 7.50 (dt, *J* = 6.2, 3.0 Hz, 20H), 7.29 – 7.21 (m, 1H). ^{13}CNMR (63 MHz, D_2O) δ 162.5, 152.8, 141.9, 135.8, 130.2, 129.7, 127.8, 126.0, 125.8, 124.4, 123.7, 117.4, 116.2, 108.4. Anal. Calcd for $C_{16}H_{11}NO_3$: 265.0739. Found: 264.0811 (M-1). GC RT 20.18 minutes.

2-(3-Methoxyphenoxy)naphthalene (305)[43] ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.85 (dq, *J* = 5.3, 2.4, 1.8 Hz, 3H), 7.54 – 7.45 (m, 5H), 6.86 – 6.75 (m, 3H), 3.81 (s, 3H). ^{13}CNMR (63 MHz, D_2O) δ 161.2, 158.6, 155.0, 134.5, 130.4, 130.2, 129.9, 127.8, 127.2, 126.6, 124.8, 120.1, 114.5, 111.3, 109.3, 105.2, 55.4. Anal. Calcd for $C_{17}H_{14}O_2$: 250.0994 Found: 249.1002 (M-1). GC RT 15.11 minutes.

2-(4-Iodophenoxy)naphthalene (307)[45]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.86 (dd, *J* = 5.7, 3.6 Hz, 3H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.44 (m, 3H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 2H). ^{13}CNMR (63 MHz, D_2O) δ 156.7, 154.5, 138.1, 133.2,

129.9, 127.7, 127.0, 126.5, 125.7, 118.2, 114.4, 108.8, 81.2. Anal. Calcd for $C_{16}H_{11}IO$: 345.9855. Found: 345.0005 (M-1). GC RT 19.38 minutes.

2-(4-Bromophenoxy)naphthalene (308)[45]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.92 (dt, *J* = 6.2, 3.3 Hz, 5H), 7.61 – 7.48 (m, 7H), 7.01 (d, *J* = 8.9 Hz, 1H). ^{13}CNMR: δ 156.4, 154.5, 133.4, 132.7, 130.3, 130.1, 128.0, 127.1, 126.6, 124.9, 119.8, 117.5, 144.4, 109.5. Anal. Calcd for $C_{16}H_{11}BrO$: 297.9993. Found: 297.0011 (M-1). GC RT 17.36 minutes.

2-(Naphthalen-2-yloxy)isoindoline-1,3-dione (309)[46]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.92 (dt, *J* = 6.0, 2.9 Hz, 7H), 7.55 (dt, *J* = 6.0, 2.9 Hz, 3H), 7.14 (d, *J* = 8.8 Hz, 1H). ^{13}CNMR (63 MHz, D_2O) δ 161.3, 150.7, 137.7, 133.4, 129.1, 128.5, 127.8, 127.1, 126.3, 125.6, 122.5, 121.6, 110.6, 104.9. Anal. Calcd for $C_{18}H_{11}NO_3$: 289.0739. Found: 288.0814 (M-1). GC RT 18.73 minutes.

1-Phenoxy-4-(trifluoromethyl)benzene (311)[7c]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.60 (d, *J* = 3.9 Hz, 4H), 7.24 (dd, *J* = 29.5, 7.2 Hz, 3H). ^{13}CNMR (63 MHz, D_2O) δ 161.2, 158.8, 128.6, 126.8, 124.1, 119.7, 118.8, 116.5. Anal. Calcd for $C_{13}H_9F_3O$: 238.0605 Found: 237.0717 (M-1). GC RT 7.48 minutes.

1,3-Dimethyl-2-(4-(trifluoromethyl)phenoxy)benzene (312)[7c]: ^{1}HNMR (250 MHz, Deuterium Oxide) δ 7.59 (d, *J* = 8.3 Hz, 1H), 7.21 (d, *J* = 6.4 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 29H), 6.85 (t, *J* = 7.4 Hz, 14H), 2.32 (s, 82H). ^{13}CNMR (63 MHz, D_2O) δ 165.0, 152.0, 128.5, 127.1, 126.1, 125.5, 123.0, 120.1, 15.6. Anal. Calcd for $C_{15}H_{13}F_3O$: 266.0918. Found: 265.1101 (M-1). GC RT 7.88 minutes.

4-(4-(Trifluoromethyl)phenoxy)benzonitrile (313)[3d]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.41 – 7.29 (m, 4H), 7.19 (dd, *J* = 29.5, 7.2 Hz, 3H). ^{13}CNMR (63 MHz, D_2O) δ 161.2, 158.8, 128.6, 126.8, 124.1, 119.7, 118.8, 116.5. Anal. Calcd for $C_{14}H_8F_3NO$: 263.0558. Found: 262.0722 (M-1). GC RT 12.87 minutes.

1-Bromo-4-(4-(trifluoromethyl)phenoxy)benzene (315)[7c]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 7.9 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 2H), 6.88 (d, *J* = 7.9 Hz, 2H). ^{13}CNMR (75 MHz, cdcl$_3$) δ 146.2, 157.6, 132.3, 127.1, 125.8, 123.4, 119.9, 117.8. Anal. Calcd for $C_{13}H_8BrF_3O$: 315.9711. Found: 315.0002 (M-1). GC RT 10.00 minutes.

1-(4-Phenoxyphenyl)ethanone (316)[43]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 6.6 Hz, 2H), 7.53 – 7.43 (m, 2H), 7.29 – 7.18 (m, 3H), 7.15 – 7.05 (m, 2H). ^{13}CNMR (63 MHz, D_2O) δ 198.2, 160.7, 159.1, 128.3, 128.0, 122.7, 119.0, 116.1, 26.3. Anal. Calcd for $C_{14}H_{12}O_2$: 212.0837. Found: 211.0901 (M-1). GC RT 9.90 minutes.

1-(4-(2,6-Dimethylphenoxy)phenyl)ethanone (317)[43]: ^{1}HNMR (250 MHz, Deuterium Oxide) δ 7.97 (d, *J* = 7.0 Hz, 2H), 7.56 (d, *J* = 7.0 Hz, 2H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.03 – 6.94 (m, 3H), 2.26 (s, 3H). ^{13}CNMR (63 MHz, D_2O) δ 192.5, 164.0, 152.2, 133.0, 130.7, 128.3, 126.8, 125.8, 123.2, 119.8, 26.3, 15.8. Anal. Calcd for $C_{16}H_{16}O_2$: 240.1150. Found: 239.1200 (M-1). GC RT 8.91 minutes.

4-(4-Acetylphenoxy)benzonitrile (318)[43]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.97 – 7.85 (m, 4H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 8.9 Hz, 2H), 2.54 (s, 3H). ^{13}CNMR (63 MHz, D_2O) δ 198.6, 160.7, 133.8, 130.6, 128.0, 119.0, 116.4, 102.1, 26.3. Anal. Calcd for $C_{15}H_{11}NO_2$: 237.0790. Found: 236.0881 (M-1). GC RT 9.12 minutes.

1-(4-(4-Bromophenoxy)phenyl)ethanone (320)[43]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 1.4 Hz, 2H), 7.33 – 7.23 (m, 4H), 6.96 (d, *J* = 3.3 Hz, 2H), 2.63 (s, 3H). ^{13}CNMR (63 MHz, D_2O) δ 198.5, 161.7, 155.1, 132.2, 130.8, 128.4, 117.2, 116.5, 115.2, 26.5. Anal. Calcd for $C_{14}H_{11}BrO_2$: 289.9942. Found: 289.0007 (M-1). GC RT 13.61 minutes.

3-Phenoxyphenol (321)[16b]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.40 – 7.31 (m, 2H), 7.25 – 7.14 (m, 4H), 6.94 (td, *J* = 7.4, 1.0 Hz, 3H), 5.29 (s, 1H). ^{13}CNMR (63 MHz, D_2O) δ 158.6, 155.4, 130.4, 129.6, 123.5, 120.7, 110.8, 107.4, 106.0. Anal. Calcd for $C_{12}H_{10}O_2$: 186.0681. Found: 187.0555 (M+1). GC RT 7.75 minutes.

3-(2,6-Dimethylphenoxy)phenol (322)[43]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.29 – 7.11 (m, 4H), 7.06 (d, *J* = 5.5 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.82 (s, 1H), 2.96 (s, 6H), 2.14 (s, 3H). ^{13}CNMR (63 MHz, D_2O) δ 156.1, 154.5, 151.1, 132.3, 131.2, 129.3, 128.3, 115.1, 114.2, 108.8, 16.5. Anal. Calcd for $C_{14}H_{14}O_2$: 214.0994. Found: 215.0887 (M+1). GC RT 6.97 minutes.

4-(3-Hydroxyphenoxy)benzonitrile (323)[43]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.1 Hz, 2H), 7.47 – 7.17 (m, 3H), 7.04 – 6.92 (m, 3H), 5.27 (s, 1H). ^{13}CNMR (63 MHz, D_2O) δ 164.4, 159.7, 155.5, 134.0, 129.3, 119.4, 117.5, 110.5, 108.8, 104.0, 103.3. Anal. Calcd for $C_{13}H_9NO_2$: 211.0633. Found: 212.0506 (M+1). GC RT 7.77 minutes.

3-(4-Bromophenoxy)phenol (325)[43]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.45 (dd, *J* = 20.0, 8.9 Hz, 4H), 7.26 – 7.20 (m, 1H), 6.95 – 6.78 (m, 3H), 5.29 (s, 1H). ^{13}CNMR (63 MHz, D_2O) δ 156.3, 155.6, 155.1, 132.3, 129.6, 120.5, 117.2, 115.3, 112.3, 104.9. Anal. Calcd for $C_{12}H_9BrO_2$: 263.9786. Found: 262.9523 (M-1). GC RT 8.59 minutes.

N,N-Dimethyl-3-phenoxyaniline (326)[43]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.27 – 7.23 (m, 2H), 7.16 (m, 4H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.78 (s, 1H), 6.74 (d, *J* = 4.4 Hz, 1H). ^{13}CNMR (63 MHz, D_2O) δ 157.9, 156.6, 148.6, 129.9, 129.6, 122.8, 119.7, 107.9, 107.1, 103.7, 40.8. Anal. Calcd for $C_{14}H_{15}NO$: 213.1154. Found: 214.1010 (M+1). GC RT 8.41 minutes.

4-(3-(Dimethylamino)phenoxy)benzonitrile (328)[43]: ^{1}HNMR (250 MHz, Deuterium Oxide) δ 7.53 (s, 2H), 7.32 – 7.21 (m, 3H), 6.81 – 6.75 (m, 1H), 6.74 (s, 1H), 6.40 (d, *J* = 2.1 Hz, 1H), 3.11 (s, 6H). ^{13}CNMR (63 MHz, D_2O) δ 160.5, 158.2, 151.7, 133.7, 128.6, 117.2, 116.0, 108.8, 107.4, 106.3, 102.1, 40.4. Anal. Calcd for $C_{15}H_{14}N_2O$: 238.1106. Found: 237.1212 (M-1). GC RT 7.01 minutes.

1-Methyl-4-phenoxybenzene (331)[45]: ^{1}HNMR (250 MHz, Deuterium Oxide) δ 7.48 (t, *J* = 7.8 Hz, 2H), 7.30 – 7.04 (m, 7H), 2.25 (s, 3H). ^{13}CNMR (63 MHz, D_2O) δ 158.5, 155.7, 133.3, 129.6, 120.5, 118.2, 115.3, 21.2. Anal. Calcd for $C_{13}H_{12}O$: 184.0888. Found: 185.0759 (M+1). GC RT 8.41 minutes.

1,3-Dimethyl-2-(p-tolyloxy)benzene (332)[3d]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.29 – 7.00 (m, 3H), 6.81 (d, *J* = 75.2 Hz, 2H), 6.55 (d, *J* = 52.9 Hz, 2H), 2.32 (s, 3H), 2.07 (s, 6H). ^{13}CNMR (63 MHz, D_2O) δ 154.5, 151.6, 132.5, 129.9, 128.8, 128.1, 124.8, 114.2, 22.9, 16.7. Anal. Calcd for $C_{15}H_{16}O$: 212.1201. Found: 213.1108 (M+1). GC RT 9.42 minutes.

4-(p-Tolyloxy)benzonitrile (333)[43]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 8.7 Hz, 2H), 7.24 – 7.11 (m, 4H), 6.81 (d, *J* = 6.4 Hz, 2H), 2.33 (s, 3H). ^{13}CNMR (63

MHz, D_2O) δ 166.9, 155.4, 133.9, 133.9, 130.5, 120.2, 118.8, 117.4, 104.8, 21.4. Anal. Calcd for $C_{14}H_{11}NO$: 209.0841. Found: 208.0735 (M-1). GC RT 14.67 minutes.

1-Bromo-4-(p-tolyloxy)benzene (335)[45]: ^{1}HNMR (300 MHz, Chloroform-*d*) δ 7.37 (dd, *J* = 24.0, 8.7 Hz, 4H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 2.35 (s, 3H). ^{13}CNMR (63 MHz, D_2O) δ 157.0, 154.4, 133.5, 132.5, 130.4,119.8, 119.2, 117.2, 115.1, 20.7. Anal. Calcd for $C_{13}H_{11}BrO$: 261.9993. Found: 261.0056 (M-1). GC RT 16.36 minutes.

CHAPTER IV
COUPLING OF ARYLBORATES TO ANILINES: APPLICATION OF ULTRASOUND TO THE CHAN-EVANS-LAM REACTION

4.1 Introduction

Aryl-aryl and aryl-phenol coupling reactions, such as the Suzuki and Ullmann reactions are important and powerful methodologies in organic chemistry. However the corresponding aryl-nitrogen coupling reaction is not as common, especially one that involves mild conditions and can use a wide spectrum of amines, anilines, and heteroarenes.[47] Traditional procedures, such as the Ullmann reactions produce modest yields, and require heat and strongly basic conditions; these can be incompatible with many amines and anilines. In the mid-1990s, researchers were able to develop a method, using palladium metal, mirroring the Suzuki reaction, to perform coupling between an aryl halide and an amine.[3e, 48] Although these reactions did not require the strong basic conditions or long reaction times of the Ullmann, they did require moderate to high heat – making the reaction incompatible for coupling thermally sensitive arenes and indoles. In the search for a C-N coupling reaction using mild conditions for pharmaceutical synthesis, the Chan-Lam reaction was developed (shortly thereafter expanded to the Chan-Evans-Lam reaction).[6a] As previously discussed in Chapter 3, this reaction uses copper(II) acetate, under anhydrous conditions, to perform the coupling reaction at room temperature. These relatively mild conditions have allowed the reaction to be applied to a variety of anilines and indoles that could not be arylated using previously published methods.[2a, 7c] The primary downsides to the Chan-Lam reaction is time, typically 24-72 hours, and the requirement that the reaction remain anhydrous.[6b]

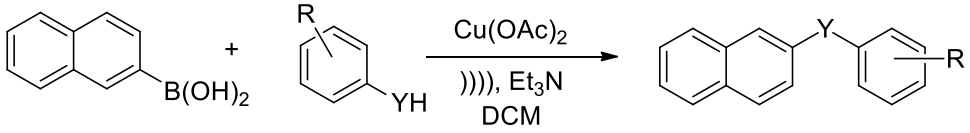
In Chapter 3, the application of ultrasound to the Chan-Evans-Lam reaction for coupling various arylborates to phenols resulted in improved reactions (decreased reaction time and increased product yields). We decided to expand that method to the N-arylation of anilines and indoles. To our knowledge ultrasound has not been applied to the Chan-Evans-Lam modified Ullmann reaction for the coupling of an aryl carbon to a nitrogen.

4.2 Results and Discussion

4.2.1 Reaction of Naphthaboronic Acid with Anilines and Indoles

Various anilines and indoles were mixed with naphthaboronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. The results are presented in **Table 4-1**.

Table 4-1 Reactions of Naphthaboronic Acid with Anilines and Indoles



Y = NR, NH

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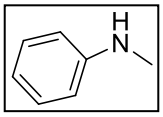
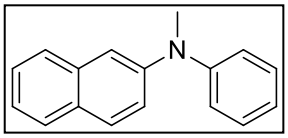
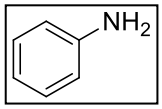
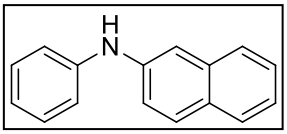
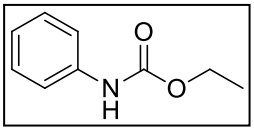
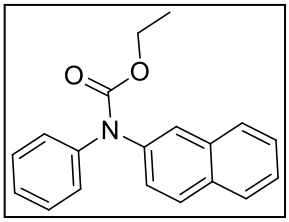
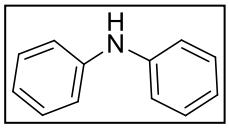
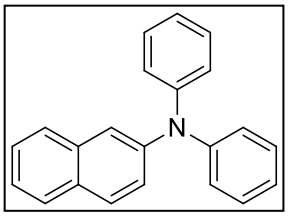
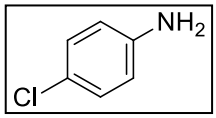
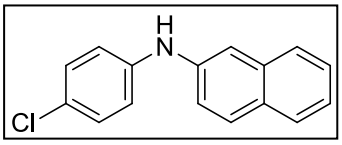
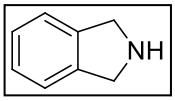
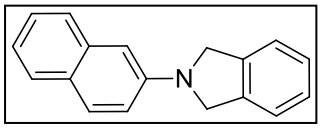
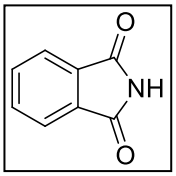
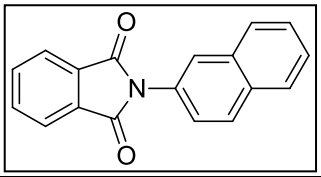
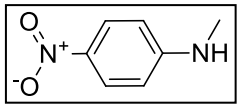
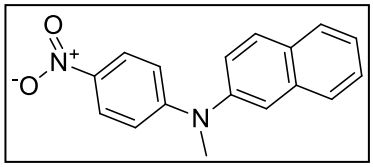
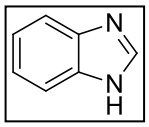
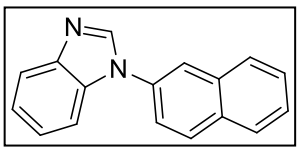
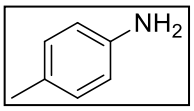
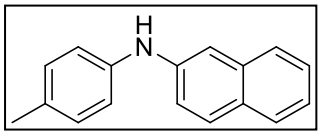
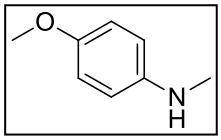
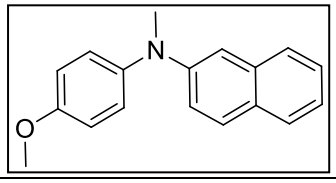
1			90	401
2			87	402
3			NR	403
4			NR	404
5			94	405
6			89	406
7			NR	407

8			96	408
9			97	409
10			95	410
11			87	411

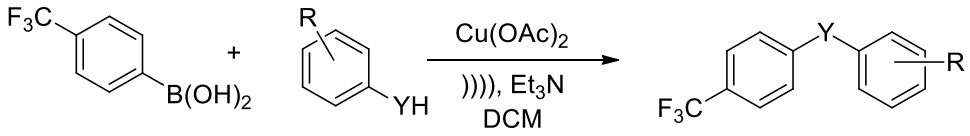
With the exception of the attempted synthesis of ethyl naphthalen-2-yl(phenyl)carbamate, N,N-diphenylnaphthalen-2-amine, and 2-(naphthalen-2-yl)isoindoline-1,3-dione, the expected coupling product was formed. No homocoupling product was detected and all unreacted naphthylboronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

The synthesis of compound 402 was repeated using a tenfold increase in the amount of all reagents and solvent. Sonication energy was increased to 20% amplitude (110 watts), and the reaction vessel was changed to a 100ml beaker. A final yield of 78% was determined, indicating that the N-arylation reaction is scalable.

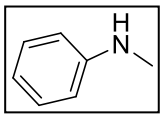
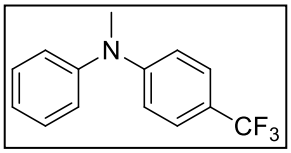
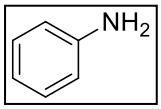
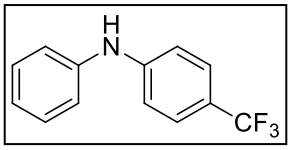
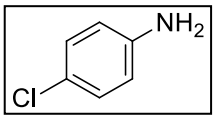
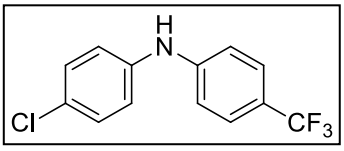
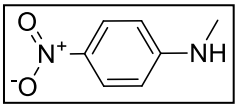
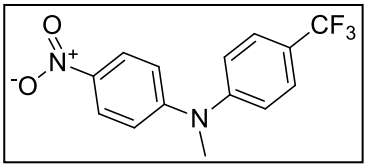
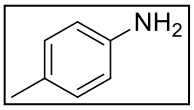
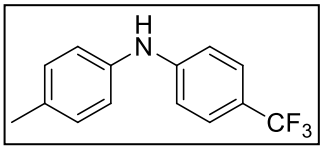
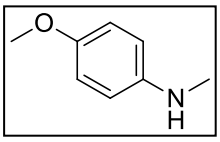
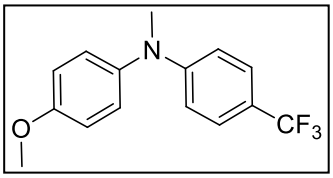
4.2.2 Reaction of (4-(Trifluoromethyl)phenyl)boronic Acid with Anilines

Various anilines and indoles were mixed with (4-(trifluoromethyl)phenyl)boronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. The reaction results are shown in **Table 4-2**.

Table 4-2 Reactions of (4-(Trifluoromethyl)phenyl)boronic Acid with Anilines



Y = NR, NH

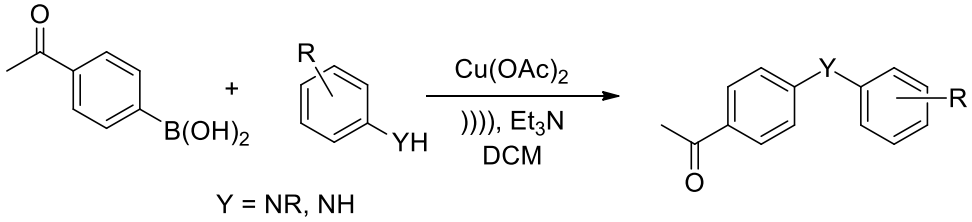
Entry	Starting Material	Product	Yield	Product
1			91	412
2			86	413
3			96	414
4			93	415
5			92	416
6			97	417

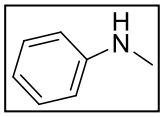
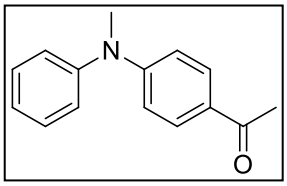
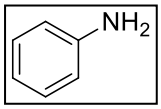
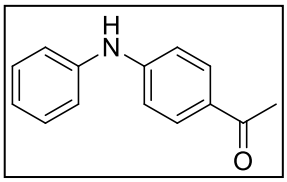
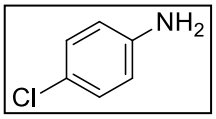
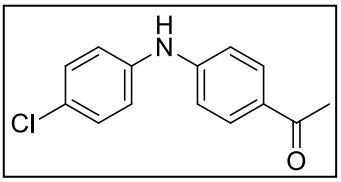
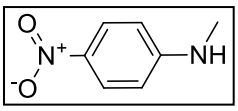
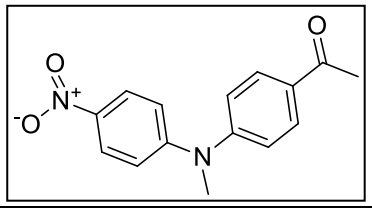
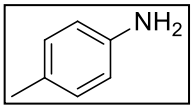
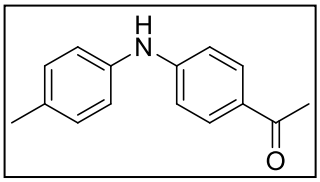
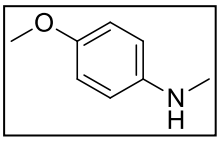
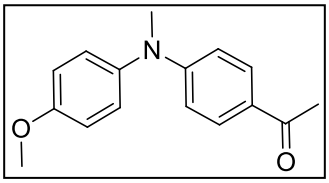
In all cases, the expected coupling product was formed. No homocoupling product was detected and all unreacted (4-(trifluoromethyl)phenyl)boronic acid remained as the boronic acid.

4.2.3 Reaction of (4-Acetylphenyl)boronic Acid with Anilines

Various anilines and indoles were mixed with (4-acetylphenyl)boronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. The reaction results are shown in **Table 4-3**.

Table 4-3 Reactions of (4-Acetylphenyl)boronic Acid with Anilines



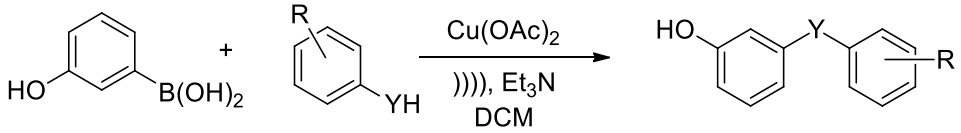
Entry	Starting Material	Product	Yield	Product
1			NR	418
2			NR	419
3			92	420
4			NR	421
5			90	422
6			93	423

With the exception of the attempted synthesis of 1-(4-(methyl(phenyl)amino)phenyl)ethanone, 1-(4-(phenylamino)phenyl)ethanone, and 1-(4-(methyl(4-nitrophenyl)amino)phenyl)ethanone, the expected coupling product was formed. No homocoupling product was detected and all unreacted (4-acetylphenyl)boronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

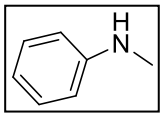
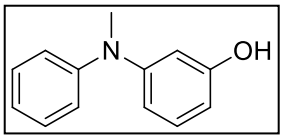
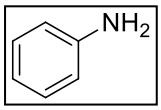
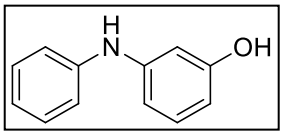
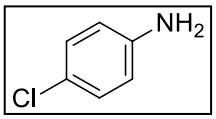
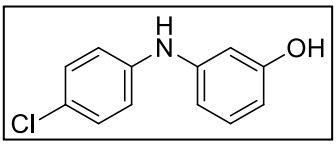
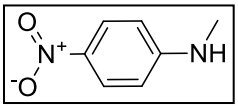
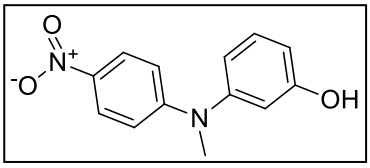
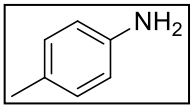
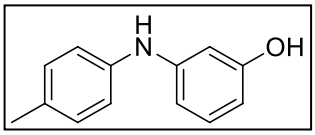
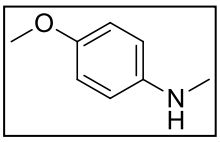
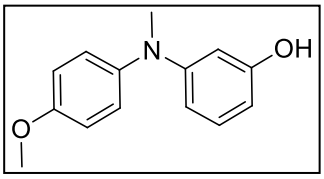
4.2.4 Reaction of (3-Hydroxyphenyl)boronic Acid with Anilines

Various anilines and indoles were mixed with (3-hydroxyphenyl)boronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. The reaction results are shown in **Table 4-4**.

Table 4-4 Reactions of (3-Hydroxyphenyl)boronic Acid with Anilines



Y = NR, NH

Entry	Starting Material	Product	Yield	Product
1			78	424
2			62	425
3			66	426
4			NR	427
5			NR	428
6			NR	429

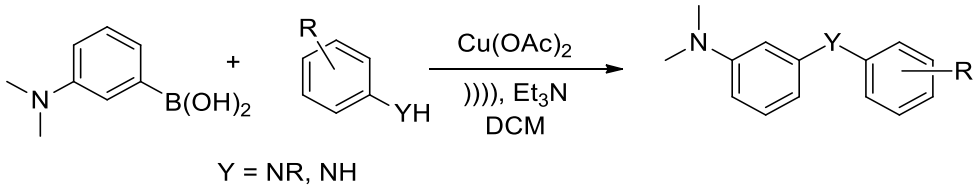
With the exception of the attempted synthesis of 3-(methyl(4-nitrophenyl)amino)phenol, 3-(p-tolylamino)phenol, and 3-((4-

methoxyphenyl)(methyl)amino)phenol, the expected coupling product was formed. No homocoupling product was detected and all unreacted (3-hydroxyphenyl)boronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

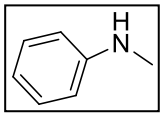
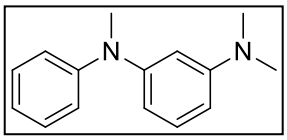
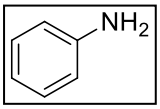
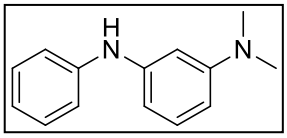
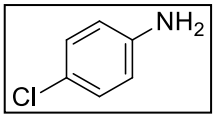
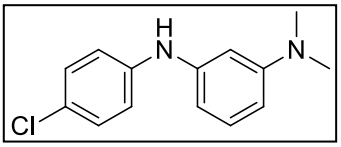
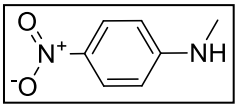
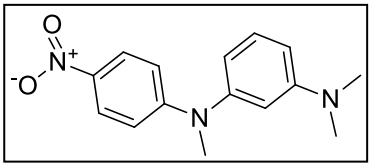
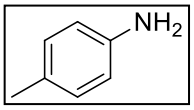
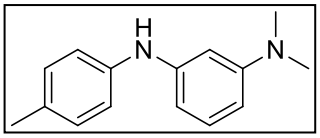
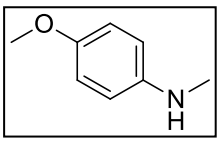
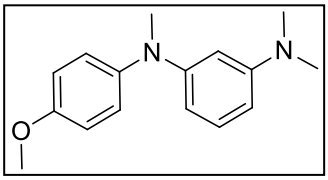
4.2.5 Reaction of (3-(Dimethylamino)phenyl)boronic Acid with Anilines

Various anilines and indoles were mixed with (3-(dimethylamino)phenyl)boronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. The reaction results are shown in **Table 4-5**.

Table 4-5 Reactions of (3-(Dimethylamino)phenyl)boronic Acid with Anilines



Y = NR, NH

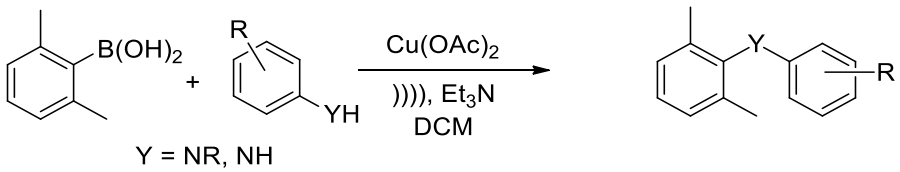
Entry	Starting Material	Product	Yield	Product
1			68	430
2			72	431
3			61	432
4			66	433
5			82	434
6			81	435

In all cases, the expected coupling product was formed. No homocoupling product was detected and all unreacted (3-(dimethylamino)phenyl)boronic acid remained as the boronic acid.

4.2.6 Reaction of (2,6-Dimethylphenyl)boronic Acid with Anilines

Various anilines and indoles were mixed with (2,6-dimethylphenyl)boronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. (**Scheme 4-1**). No products were detected. This was verified with additional experiments. An additional set of experiments were carried out using 6 hours of ultrasonic radiation, again no product formed.

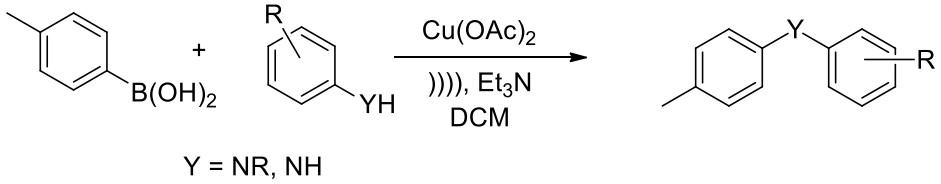
Scheme 4-1 Reaction of (2,6-Dimethylphenyl)boronic Acid with Anilines

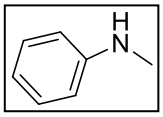
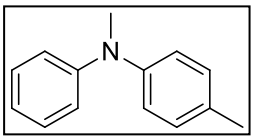
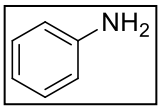
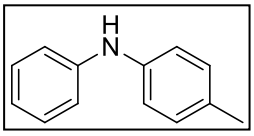
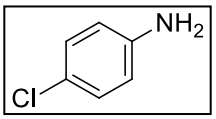
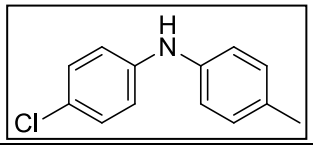
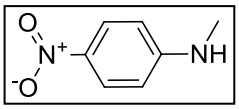
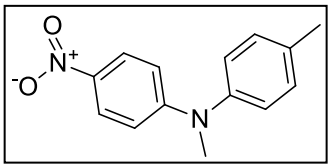
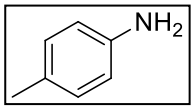
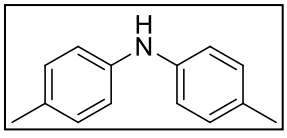
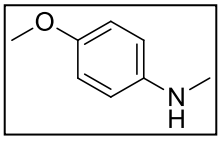
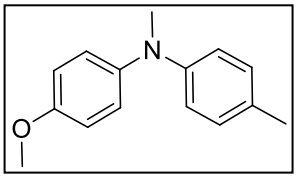


4.2.7 Reaction of p-Tolylboronic Acid with Anilines

Various anilines and indoles were mixed with p-tolylboronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. The reaction results are shown in **Table 4-6**.

Table 4-6 Reactions of p-Tolylboronic Acid with Anilines



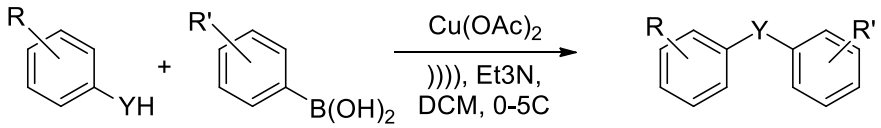
Entry	Starting Material	Product	Yield	Product
1			93	436
2			67	437
3			74	438
4			NR	439
5			90	440
6			96	441

With the exception of the attempted synthesis of N,4-dimethyl-N-(4-nitrophenyl)aniline, the expected coupling product was formed. No homocoupling

product was detected and all unreacted p-tolylboronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

In an attempt to evaluate the electronic effects of the substituent groups on the reaction, the yields were plotted against the reported sigma values, **Table 4-7**:

Table 4-7 Plot of Reactant Sigma Values correlated with Product Yield



Y = NH or NMe

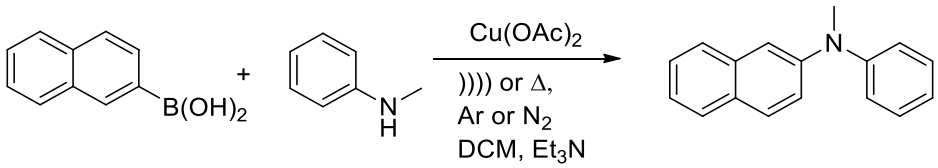
Y	R ↓ R' →	meta -OH	meta -NMe2	para -CH3	para -C(O)CH3	para -CF3
NH	para -CH3	0	82	90	90	92
NMe	para -OCH3	0	81	96	93	97
NMe	H	78	68	93	0	91
NH	H	62	72	67	0	86
NH	para -Cl	66	61	74	92	96
NMe	para -NO2	0	66	0	0	93

The data indicate that the highest product yields occur when the boronic acid contains an electron withdrawing group, while the aniline has a sigma value close to zero.

4.2.8 Mechanistic Study

The method used in this Chapter, parallels that of Chapter 3 (please see Section 3.2.8 for all relevant background information). A series of experiments were conducted and summarized in **Table 4-8**. This series was designed to test for the presence of copper(I) acetate as well as the possible formation of free radicals. All experiments were conducted as described in Section 2.2.4.

Table 4-8 Summary of Mechanism Investigation Experiments



Entry	Reaction Conditions	Product Yield
1	Naphthylboronic acid, N-methylaniline, R.T., 72 hours	72
2	Naphthylboronic acid, N-methylaniline, ultrasound 4 hours	92
3	Naphthylboronic acid, N-methylaniline, 5eq galvinoxyl R.T., 72 hours	69
4	Naphthylboronic acid, N-methylaniline, 5eq galvinoxyl ultrasound 4 hours	90

It is not possible to conduct an ultrasound experiment within an EPR, so to determine if copper(I) acetate is produced, scanning powder-x-ray diffraction was employed. The pXRD analysis revealed that all samples displayed two theta peaks associated with copper(I) acetate post reaction (2θ: 4.3, 7.2, 18, 26.7, 37, 42, 44.8; as compared to the copper(I) standard. The added galvinoxyl had no impact on the

reaction product yield. This evidence supports the postulation that ultrasound has no effect on the reaction mechanism.

4.3 Conclusion

The application of ultrasound to the Chan-Lam-Evans modified Ullmann reaction for the N-arylation of various anilines and indoles has proven successful. Although the original reaction does not call for the addition of energy, ultrasound dramatically decreased the reaction time from 72 hours to 4 hours, while improving the product yields (60-100%), and maintaining the mild reaction conditions. Of particular interest is the successful coupling of naphthaboronic acid to isoindoline (entry 6, Table 4-1), as this molecule is thermally sensitive. The resulting product yields indicates that there is an electronic effect related to the arylboronic acid, which may warrant additional study and further method development. Lam et al. report that N-arylation does not occur in some isolated cases and attributes the lack of reaction to a possible amine base affect.[6a, 7c] With the exception of Section 3.2.6, experiments that did not produce any yields are similar to the unsuccessful reactions reported by Lam.

4.4 Experimental Details

4.4.1 General Considerations

All glassware was dried at 120 °C and flushed with dry nitrogen prior to use. All chemicals were purchased from commercial sources and used as received. Gas Chromatography-Mass Spectroscopy studies were carried out on a Hewlett Packard: HP 6890 series GC System with 5973 Mass Selective Detector; Column: HP-5 30 m x 0.25 mm x 0.25 μm; Gas (He) flow 0.8 ml/min; temperature program: flow 0.8 ml/min,

initial temperature 90 °C for 1 minute, a temperature ramp of 15 °/minute up to 200 °C, then a temperature ramp of 5 °/min up to 250 °C for 10 minutes. All samples were purified using column chromatography (anhydrous sodium sulfate and 60 Å 230-400 mesh silica gel), and then recrystallized.

All sonication experiments were carried out using a Fisher Scientific Model 550 Sonic Dismemborator, employing a 0.5 inch horn sonicator and a 1 inch by 2 inch cylindrical reaction vessel. All individual reactions were carried out in new borsite glass vessels. Reaction vessel external temperature was maintained at 0-5 °C with an ice water bath.

4.4.2 Representative Procedure for the Synthesis of N-methyl-N-phenylnaphthalen-2-amine

Naphthylboronic acid (0.25 g, 1.5 mmol) was added to N-methylaniline (0.11 g, 1 mmol) in 15ml of DCM. Copper(II) acetate (0.36 g, 2.0 mmol) was then added along with triethylamine (0.5g, 5.0 mmol), and the dismemberator horn placed in the reaction vessel. The sonicator was set to 55 watts and the reaction was allowed to proceed for 4 hours (1 minute pulse with a 3 second rest). Post reaction, the product was isolated by column chromatography. Product yields were determined by weight and purity was confirmed by GC/MS and NMR.

4.4.3 Characterization of Compounds 401-441

^{1}H NMR and ^{13}C NMR spectra were recorded either at 250 and 63 MHz or 300 and 75 MHz respectively. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra were referenced to TMS and the d-chloroform solvent shift. High quality mass spectrometry

was carried out using a Qstar electron spray ionization mass spectrometer, in either positive (M+1) or negative mode (M-1), ionization energy of ±5000 e/v, injection rate of 20 μl/min.

N-Methyl-N-phenylnaphthalen-2-amine (401)[49]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.82 (dq, *J* = 6.2, 2.9 Hz, 4H), 7.66 (t, *J* = 8.3 Hz, 2H), 7.45 (dt, *J* = 6.3, 3.1 Hz, 3H), 7.29 (d, *J* = 7.3 Hz, 2H), 7.12 – 6.96 (m, 3H), 3.38 (s, 3H). ^{13}C NMR (63 MHz, D_2O) δ 149.9, 143.6, 136.8, 129.0, 128.3, 127.4, 127.3, 127.0, 125.7, 118.2, 116.0, 106.0, 45.2. Anal. Calcd for $C_{17}H_{15}N$: 233.1204. Found: 234.0997 (M+1). GC RT 15.76 minutes.

N-Phenylnaphthalen-2-amine (402)[49]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.86 – 7.78 (m, 3H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.44 – 7.35 (m, 3H), 7.27 (t, *J* = 6.3 Hz, 1H), 7.12 – 7.00 (m, 2H), 4.20 (s, 1H). ^{13}C NMR (63 MHz, D_2O) δ 142.7, 133.1, 129.1, 128.8, 127.6, 126.2, 125.6, 123.1, 120.9, 111.0. Anal. Calcd for $C_{16}H_{13}N$: 219.1048. Found: 220.0879 (M+1). GC RT 16.50 minutes.

N-(4-Chlorophenyl)naphthalen-2-amine (405)[49]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.94 – 7.63 (m, 6H), 7.50 (dd, *J* = 6.3, 3.3 Hz, 2H), 7.34 (t, *J* = 6.9 Hz, 1H), 7.25 (d, *J* = 2.2 Hz, 2H), 3.69 (s, 1H). ^{13}C NMR (75 MHz, $cdcl_3$) δ 144.9, 141.4, 133.2, 128.8, 127.6, 126.3, 125.6, 123.4, 122.5, 118.9, 115.9, 111.6. Anal. Calcd for $C_{16}H_{12}ClN$: 253.0658. Found: 252.0944 (M-1). GC RT 20.17 minutes.

2-(Naphthalen-2-yl)isoindoline(406)[49]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.87 – 7.63 (m, 5H), 7.41 (s, 4H), 7.40 – 7.37 (m, 1H), 4.57 (s, 2H). ^{13}C NMR (75 MHz, $cdcl_3$) δ 144.9, 137.7, 135.2, 129.1, 127.8, 125.5, 121.6, 115.1, 105.0, 53.8. Anal. Calcd for $C_{18}H_{15}N$: 245.1204. Found: 256.1310 (M+1). GC RT 22.56 minutes.

N-Methyl-N-(4-nitrophenyl)naphthalen-2-amine (408)[49]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 9.2 Hz, 2H), 7.84 (dd, *J* = 6.2, 3.3 Hz, 6H), 7.47 (dd, *J* = 6.3, 3.3 Hz, 3H), 6.49 (d, *J* = 9.2 Hz, 2H), 2.90 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 154.3, 143.5, 137.9, 133.5, 129.0, 127.9, 126.4, 125.9, 122.8, 120.3, 118.1, 110.7, 42.3. Anal. Calcd for $C_{17}H_{14}N_2O_2$: 278.1055. Found: 277.1112 (M-1). GC RT 11.60 minutes.

1-(Naphthalen-2-yl)-1H-benzo[d]imidazole (409)[46]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 14.6, 5.1 Hz, 2H), 7.75 (t, *J* = 8.2 Hz, 2H), 7.49 (dd, *J* = 6.6, 2.8 Hz, 3H), 5.99 – 5.81 (m, 4H), 2.99 – 2.88 (m, 2H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 143.0, 142.8, 134.2, 134.0, 133.8, 133.0, 132.8, 130.0, 129.1, 127.3, 122.9, 122.5, 121.7, 119.4, 110.7. Anal. Calcd for $C_{17}H_{12}N_2$: 244.1000. Found: 245.1152 (M+1). GC RT 21.19 minutes.

N-(p-Tolyl)naphthalen-2-amine (410)[24j]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.82 (dq, *J* = 6.2, 2.9 Hz, 4H), 7.49 – 7.42 (m, 2H), 7.28 (dd, *J* = 8.5, 7.3 Hz, 5H), 4.21 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 146.3, 140.1, 130.5, 129.6, 128.0, 125.1, 119.9, 118.6, 118.1, 116.6, 107.0, 20.4. Anal. Calcd for $C_{17}H_{15}N$: 233.1204. Found: 234.1178 (M+1). GC RT 14.96 minutes.

N-(4-Methoxyphenyl)-N-methylnaphthalen-2-amine (411)[18]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.87 - 7.70 (m, 4H), 7.51 - 7.27 (m, 4H), 6.85 (d, *J* = 7.9 Hz, 2H), 4.56 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 152.4, 144.7, 142.6, 133.5, 129.6, 127.9, 126.4, 125.9, 122.6, 120.1, 116.2, 114.6, 108.4, 55.9, 43.5. Anal. Calcd for $C_{18}H_{17}NO$: 263.1310. Found: 264.1078 (M+1). GC RT 19.83 minutes.

N-Methyl-N-phenyl-4-(trifluoromethyl)aniline (412)[49]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.32 (d, *J* = 1.1 Hz, 2H), 7.30 – 7.29 (m, 2H), 6.84 (t, *J* = 1.1 Hz, 1H), 6.72 – 6.70 (m, 4H), 3.15 (s, 1H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 152.1, 149.2, 129.1, 125.5, 123.7, 121.6, 117.2, 112.4, 44.8. Anal. Calcd for $C_{14}H_{12}F_3N$: 251.0922. Found: 250.1075 (M-1). GC RT 9.58 minutes.

N-Phenyl-4-(trifluoromethyl)aniline (413)[49]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.41 (d, *J* = 8.4 Hz, 4H), 7.29 – 7.06 (m, 4H), 6.70 (t, *J* = 7.2 Hz, 1H), 3.53 (s, 1H). ^{13}C NMR (63 MHz, D_2O) δ 147.6, 146.2, 128.9, 126.4, 122.5, 119.7, 118.2. Anal. Calcd for $C_{13}H_{10}F_3N$: 237.0765. Found: 236.0908 (M-1). GC RT 12.69 minutes.

4-Chloro-N-(4-(trifluoromethyl)phenyl)aniline (414)[3e]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 (d, *J* = 7.4 Hz, 2H), 7.20 (d, *J* = 7.3 Hz, 4H), 7.04 (d, *J* = 6.3 Hz, 2H), 4.04 (s, 1H).). ^{13}C NMR (63 MHz, D_2O) δ 144.5, 139.8, 129.5, 129.1, 128.6, 126.4, 122.7, 120.7. Anal. Calcd for $C_{13}H_9ClF_3N$: 271.0376. Found: 270.0500 (M-1). GC RT 16.11 minutes.

N-Methyl-4-nitro-N-(4-(trifluoromethyl)phenyl)aniline (415)[48a]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 8.05 (d, *J* = 8.9 Hz, 2H), 7.75 – 7.61 (m, 2H), 7.30 – 7.09 (m, 2H), 6.48 (d, *J* = 8.6 Hz, 2H), 3.62 (s, 1H). ^{13}C NMR (63 MHz, D_2O) δ 156.7, 147.2, 137.9, 133.5, 131.2, 125.9, 125.4, 119.4, 113.9, 43.4. Anal. Calcd for $C_{14}H_{11}F_3N_2O_2$: 296.0773. Found: 295.0972 (M-1). GC RT 7.04 minutes.

4-Methyl-N-(4-(trifluoromethyl)phenyl)aniline (416)[48a]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.46 – 7.21 (m, 6H), 7.14 (d, *J* = 6.4 Hz, 2H), 4.12 (s, 1H), 2.31 (s,

3H). ^{13}C NMR (63 MHz, D_2O) δ 147.9, 138.8, 132.7, 129.9, 126.4, 123.3, 120.9, 20.9. Anal. Calcd for $C_{14}H_{12}F_3N$: 251.0922. Found: 250.1122 (M-1). GC RT 13.53 minutes.

4-Methoxy-N-methyl-N-(4-(trifluoromethyl)phenyl)aniline (417)[16e]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.23 (d, *J* = 1.9 Hz, 2H), 6.82 (d, *J* = 1.9 Hz, 2H), 6.70 – 6.50 (m, 4H), 3.79 (s, 3H), 3.25 (s, 1H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 153.5, 152.0, 143.6, 126.2, 125.3, 120.2, 116.2, 55.9, 42.0. Anal. Calcd for $C_{15}H_{14}F_3NO$: 281.1027. Found: 280.1257 (M-1). GC RT 6.67 minutes.

1-(4-((4-Chlorophenyl)amino)phenyl)ethanone (420)[16b]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.93 (d, *J* = 7.1 Hz, 2H), 7.54 – 7.40 (m, 4H), 7.25 (d, *J* = 8.9 Hz, 2H), 3.76 (s, 1H), 2.49 (s, 3H). ^{13}C NMR (63 MHz, D_2O) δ 198.2, 145.0, 141.0, 128.7, 128.3, 128.0, 122.3, 121.2, 115.9, 26.3. Anal. Calcd for $C_{14}H_{12}ClNO$: 245.0607. Found: 244.0779 (M-1). GC RT 7.79 minutes.

1-(4-(p-Tolylamino)phenyl)ethanone (422)[16b]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 7.3 Hz, 2H), 7.54 (dd, *J* = 24.0, 7.2 Hz, 4H), 7.34 (d, *J* = 7.9 Hz, 2H), 3.36 (s, 1H), 2.63 (s, 1H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 196.4, 149.2, 137.9, 130.6, 129.7, 121.5, 113.8, 26.6, 20.3. Anal. Calcd for $C_{15}H_{15}NO$: 225.1154. Found: 226.0997 (M+1). GC RT 8.91 minutes.

1-(4-((4-Methoxyphenyl)(methyl)amino)phenyl)ethanone (423)[16b]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.59 – 7.40 (m, 4H), 6.55 (d, *J* = 8.0 Hz, 2H), 3.72 (s, 3H), 3.29 (s, 1H), 2.57 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 198.8, 153.0, 151.8, 140.8, 128.3, 128.0, 120.1, 120.0, 114.5, 55.4, 40.0, 26.2. Anal. Calcd for $C_{16}H_{17}NO_2$: 255.1259. Found: 256.1119 (M+1). GC RT 6.57 minutes.

3-(Methyl(phenyl)amino)phenol (424)[3a]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.19 – 7.12 (m, 2H), 6.82 (t, *J* = 8.3 Hz, 1H), 6.73 – 6.65 (m, 2H), 6.55 (d, *J* = 8.6 Hz, 2H), 6.33 (d, *J* = 2.4 Hz, 1H), 6.10 (s, 1H), 5.11 (s, 1H), 3.15 (s, 1H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 156.1, 149.1, 129.3, 129.0, 119.8, 117.1, 115.2, 112.3, 102.7, 46.2. Anal. Calcd for $C_{13}H_{13}NO$: 199.0997. Found: 198.1009 (M-1). GC RT 7.17 minutes.

3-(Phenylamino)phenol (425)[50]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.13 (dt, *J* = 15.7, 7.8 Hz, 5H), 7.00 – 6.95 (m, 1H), 6.73 (t, *J* = 7.2 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 6.40 (s, 1H), 5.71 (s, 1H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 157.8, 146.3, 143.8, 128.1, 127.8, 123.2, 122.0, 110.2, 109.1, 105.3. Anal. Calcd for $C_{12}H_{11}NO$: 185.0841. Found: 184.0994 (M-1). GC RT 6.62 minutes.

3-((4-Chlorophenyl)amino)phenol (426)[50]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 2.0 Hz, 2H), 7.44 (q, *J* = 2.6, 2.2 Hz, 3H), 6.95 (d, *J* = 1.6 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.88 (s, 1H), 5.64 (s, 1H), 4.18 (s, 1H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 160.8, 148.8, 144.1, 129.3, 128.9, 124.8, 122.7, 109.4, 108.1, 104.4. Anal. Calcd for $C_{12}H_{10}ClNO$: 219.0451. Found: 218.0661 (M-1). GC RT 5.19 minutes.

N1,N1,N3-Trimethyl-N3-phenylbenzene-1,3-diamine (430)[51]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.23 (dt, *J* = 15.4, 8.3 Hz, 3H), 6.72 (dt, *J* = 14.0, 7.9 Hz, 4H), 6.61 (d, *J* = 7.5 Hz, 1H), 6.46 (s, 1H), 3.32 (s, 1H), 2.95 (s, 1H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 155.6, 150.2, 149.1, 129.6, 129.0, 120.0, 118.8, 107.0, 104.9, 41.3, 40.5. Anal. Calcd for $C_{15}H_{18}N2$: 226.1470. Found: 225.1001 (M-1). GC RT 7.92 minutes.

N1,N1-Dimethyl-N3-phenylbenzene-1,3-diamine (431)[51]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.20 (dt, *J* = 14.5, 6.5 Hz, 4H), 7.09 (dd, *J* = 13.0, 8.1 Hz, 3H), 6.88 (t, *J*

= 7.2 Hz, 1H), 6.64 (d, *J* = 20.3 Hz, 1H), 6.48 (s, 1H), 4.10 (s, 1H), 2.93 (s, 6H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 155.5, 143.8, 138.1, 129.7, 129.2, 120.4, 117.6, 112.6, 106.7, 106.0, 40.5. Anal. Calcd for $C_{14}H_{16}N_2$: 212.1313. Found: 211.1219 (M-1). GC RT 9.51 minutes.

N1-(4-Chlorophenyl)-N3,N3-dimethylbenzene-1,3-diamine (432)[52]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.83 (d, *J* = 7.1 Hz, 2H), 7.45 (d, *J* = 6.6 Hz, 2H), 7.27 – 7.03 (m, 2H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.43 (s, 1H), 4.11 (s, 1H), 2.89 (s, 6H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 149.9, 141.3, 139.6, 128.6, 128.3, 127.7, 123.3, 111.9, 104.3, 39.8. Anal. Calcd for $C_{14}H_{15}ClN_2$: 246.0924. Found: 245.1008 (M-1). GC RT 5.20 minutes.

N1,N1,N3-Trimethyl-N3-(4-nitrophenyl)benzene-1,3-diamine (433)[18]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 8.9 Hz, 2H), 7.29 – 7.20 (m, 1H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 9.1 Hz, 1H), 6.44 (s, 1H), 3.13 (s, 1H), 2.94 (s, 6H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 158.3, 156.4, 147.6, 133.3, 129.0, 126.4, 120.1, 112.6, 105.0, 43.0, 40.6. Anal. Calcd for $C_{15}H_{17}N_3O_2$: 271.1321. Found: 270.1259 (M-1). GC RT 11.87 minutes.

N1,N1-Dimethyl-N3-(p-tolyl)benzene-1,3-diamine (434)[18]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 6.4 Hz, 1H), 7.18 – 7.06 (m, 2H), 7.06 – 6.97 (m, 2H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.60 (s, 1H), 4.14 (s, 1H), 2.97 (s, 6H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 151.3, 137.4, 129.8, 128.5, 120.6, 110.2, 105.0, 41.7, 21.1. Anal. Calcd for $C_{15}H_{18}N_2$: 226.1470. Found: 225.1301 (M-1). GC RT 10.20 minutes.

N1-(4-Methoxyphenyl)-N1,N3,N3-trimethylbenzene-1,3-diamine (435)[48a]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.05 – 7.02 (m, 1H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 2.2 Hz, 1H), 6.52 (d, *J* = 8.3 Hz, 2H), 6.26 (d, *J* = 2.3 Hz, 1H), 6.20 (s, 1H), 3.75 (s, 3H), 3.23 (s, 1H), 2.90 (s, 6H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 151.9, 151.9, 150.5, 142.5, 128.8, 121.1, 116.4, 105.9, 104.1, 55.6, 42.8, 40.3. Anal. Calcd for $C_{16}H_{20}N_2O$: 256.1576. Found: 255.1431 (M-1). GC RT 12.42 minutes.

N,4-Dimethyl-N-phenylaniline (436)[49]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.06 (d, *J* = 2.1 Hz, 2H), 7.04 (d, *J* = 1.2 Hz, 2H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.55 (d, *J* = 0.9 Hz, 2H), 6.48 (d, *J* = 1.1 Hz, 2H), 3.17 (s, 1H), 2.68 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 149.3, 148.2, 129.9, 129.2, 122.5, 117.2, 112.4, 45.3, 21.6. Anal. Calcd for $C_{14}H_{15}N$: 197.1204. Found: 196.1087 (M-1). GC RT 11.57 minutes.

4-Methyl-N-phenylaniline (437)[24j]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.63 – 6.06 (m, 9H), 3.64 (s, 1H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 142.6, 138.6, 130.6, 129.2, 128.4, 122.6, 121.3, 118.9, 23.4. Anal. Calcd for $C_{12}H_{10}ClNO$: 219.0451. Found: 218.0661 (M-1). GC RT 5.19 minutes.

4-Chloro-N-(p-tolyl)aniline (438)[52]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.48 – 7.36 (m, 4H), 7.09 (d, *J* = 7.3 Hz, 2H), 4.04 (s, 1H), 2.80 (s, 3H). ^{13}C NMR (63 MHz, D_2O) δ 144.1, 142.4, 129.9, 129.0, 126.6, 125.1, 119.9, 22.1. Anal. Calcd for $C_{13}H_{12}ClN$: 217.0658. Found: 216.0771 (M-1). GC RT 5.19 minutes.

di-p-Tolylamine (440)[24j]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.29 (d, *J* = 7.9 Hz, 4H), 7.21 (d, *J* = 7.4 Hz, 4H), 3.52 (s, 1H), 2.52 (s, 6H). ^{13}C NMR (63 MHz, D_2O) δ

141.07, 130.04, 129.98, 129.40, 117.80, 20.51. Anal. Calcd for $C_{14}H_{15}N$: 197.1204. Found: 196.1107 (M-1). GC RT 14.46 minutes.

4-Methoxy-N-methyl-N-(p-tolyl)aniline (441)[49]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.02 (d, *J* = 8.9 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.55 (d, *J* = 8.4 Hz, 4H), 3.77 (s, 3H), 3.21 (s, 1H), 2.27 (s, 3H). ^{13}C NMR (63 MHz, D_2O) δ 155.25, 147.33, 142.59, 129.59, 129.24, 121.22, 120.49, 114.49, 55.42, 40.31, 20.63. Anal. Calcd for $C_{15}H_{17}NO$: 227.1310. Found: 226.1214 (M-1). GC RT 8.60 minutes.

CHAPTER V
COUPLING OF ARYLBORATES TO THIOLS: APPLICATION OF ULTRASOUND TO THE CHAN-EVANS-LAM REACTION

5.1 Introduction

Like many carbon-heteroatom couplings, historically the principal method for the formation of a C-S bond was the Ullmann condensation reaction.[2a] However, the method is not applicable to the synthesis of thermally sensitive sulfides, many of which have gained prominence in the pharmaceutical industry.[7a] The discovery of the Buchwald–Hartwig coupling reaction provided an alternative to the Ullmann reaction.[6b] However the Buchwald-Hartwig still requires a strong inorganic base, an aryl halide, and elevated temperatures (although somewhat lower than temperatures required by the Ullmann reaction), while still producing low to moderate product yields. Another negative aspect of these reactions is the required use of an aryl halide to perform the coupling reaction. Heterocyclic iodoarenes have a tendency to decompose before undergoing reaction.[7a]

Following the successful application of the Chan-Evans-Lam reaction to O-arylation of phenols, the reaction was applied to the S-arylation of thiols, with good success.[6b, 7a] The new protocol provides a major improvement over the prior methods by using catalytic or low stoichiometric amounts of copper salt, the use of a milder amine base, and being run at room temperature instead of requiring high heat.[6b] However the Chan-Evans-Lam reaction still requires 24-72 hours and an anhydrous conditions, while producing only modest product yields.[6b]

Chapter 3 and 4 outlined the successful application of ultrasound to the Chan-Evans-Lam reaction, for the coupling various arylborates to phenols, anilines, and

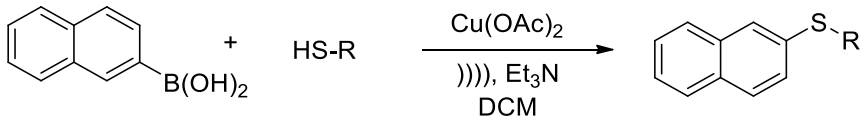
indoles, resulting in significant improvements (decreased reaction time and increased product yields). We decided to expand that newly developed method to the S-arylation of thiols. To our knowledge ultrasound has not been applied to the Chan-Evans-Lam modified Ullmann reaction for the coupling of aryl carbon to a sulfur.

5.2 Results and Discussion

5.2.1 Reaction of Naphthaboronic Acid with Thiols

Various thiols and thiophenols were mixed with naphthaboronic acid in DCM, in the presence of copper(II) acetate and triethylamine. The reaction results are presented in **Table 5-1**.

Table 5-1 Reactions of Naphthaboronic Acid with Thiols



R = alkyl or aryl

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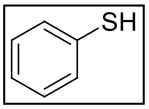
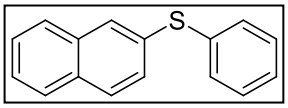
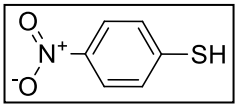
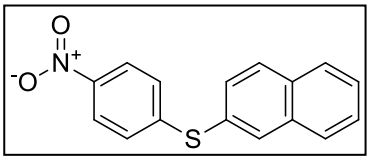
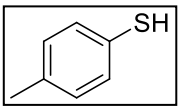
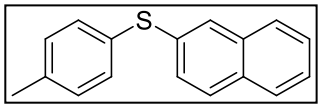
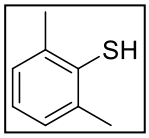
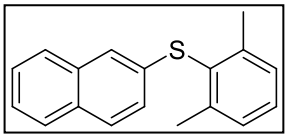
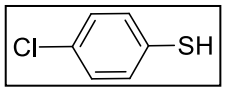
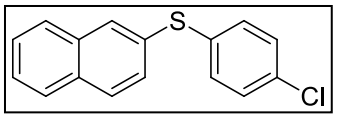
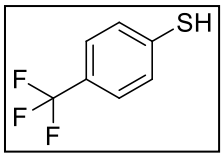
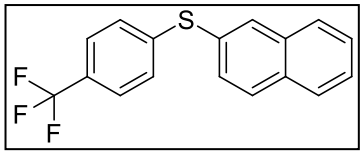
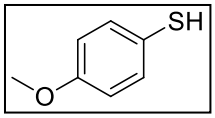
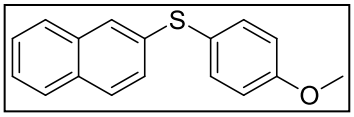
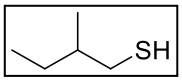
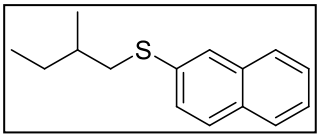
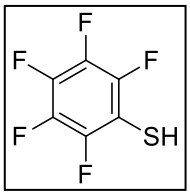
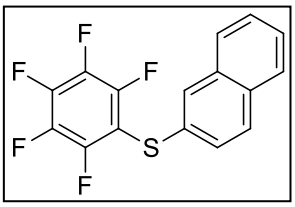
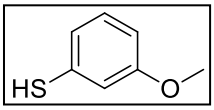
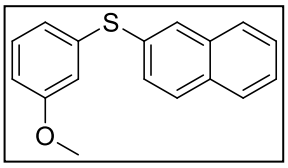
1			92	501
2			88	502
3			94	503
4			93	504
5			91	505
6			92	506
7			95	507
8			98	508

9			95	509
10			NR	510

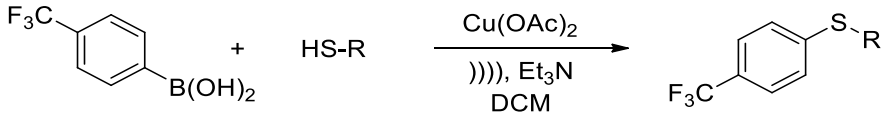
With the exception of the attempted synthesis of (3-methoxyphenyl)(naphthalen-2-yl)sulfane, the expected product was formed. There was no homocoupling products were detected, and all unreacted naphthaboronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

The synthesis of compound 501 was repeated using a tenfold increase in the amount of all reagents and solvent. Sonication energy was increased to 20% amplitude (110 watts), and the reaction vessel was changed to a 100ml beaker. A final yield of 87% was determined, indicating that the S-arylation reaction is scalable.

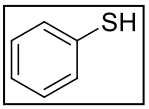
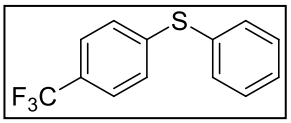
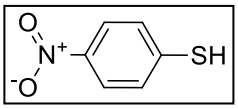
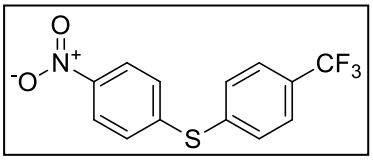
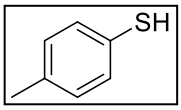
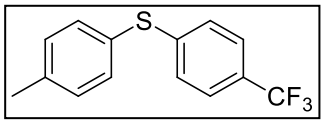
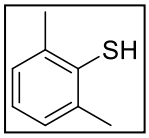
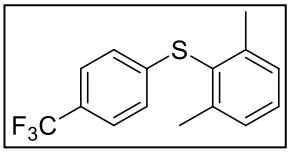
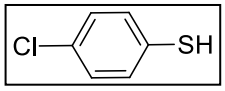
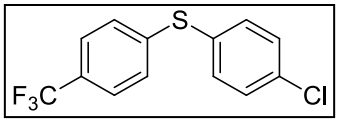
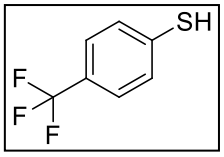
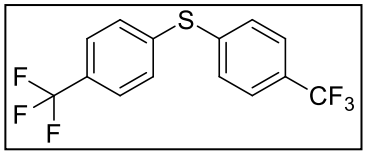
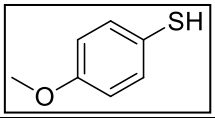
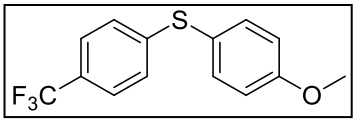
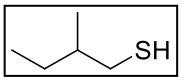
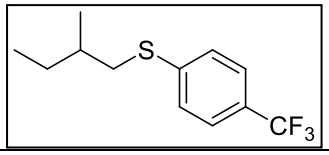
5.2.2 Reaction of (4-(Trifluoromethyl)phenyl)boronic Acid with Thiols

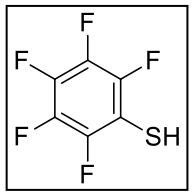
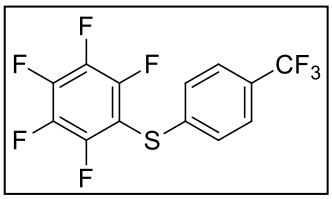
Various thiols and thiophenols were mixed with (4-(trifluoromethyl)phenyl)boronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. The reaction results are presented in **Table 5-2**.

Table 5-2 Reactions of (4-(Trifluoromethyl)phenyl)boronic Acid with Thiols



R = alkyl or aryl

Entry	Starting Material	Product	Yield	Product
1			95	511
2			91	512
3			98	513
4			NR	514
5			92	515
6			NR	516
7			NR	517
8			94	518

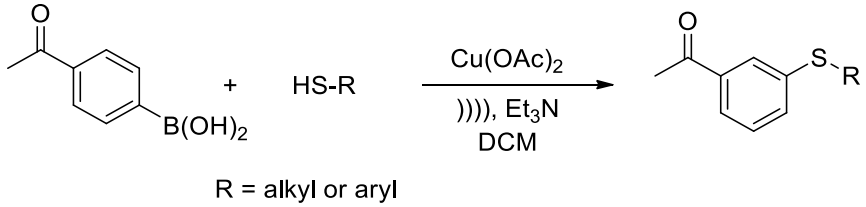
9			98	519

With the exception of the attempted synthesis of (2,6-dimethylphenyl)(4-(trifluoromethyl)phenyl)sulfane, bis(4-(trifluoromethyl)phenyl)sulfane, and (4-methoxyphenyl)(4-(trifluoromethyl)phenyl)sulfane, the expected product was formed. There was no homocoupling products were detected, and all unreacted (4-(trifluoromethyl)phenyl)boronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

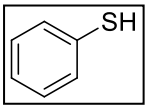
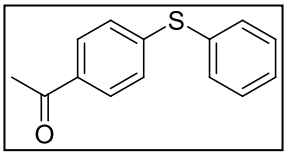
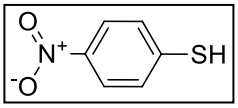
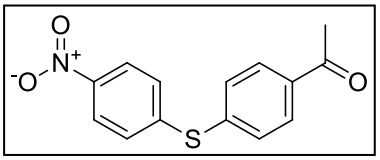
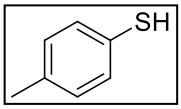
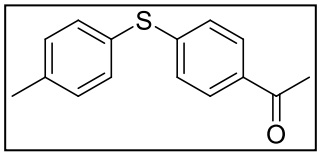
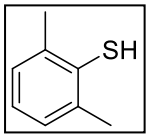
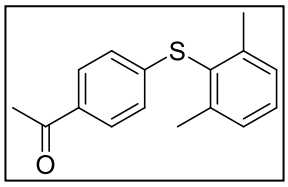
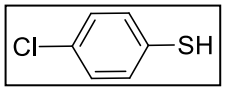
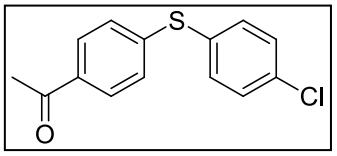
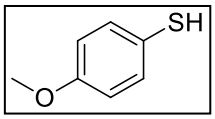
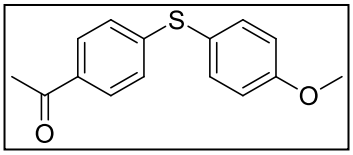
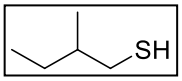
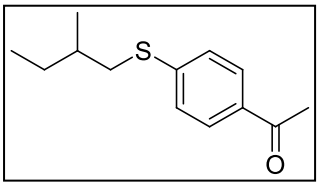
5.2.3 Reaction of (4-Acetylphenyl)boronic Acid with Thiols

Various thiols and thiophenols were mixed with (4-acetylphenyl)boronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. The reaction results are shown in **Table 5-3**.

Table 5-3 Reactions of (4-Acetylphenyl)boronic Acid with Thiols



R = alkyl or aryl

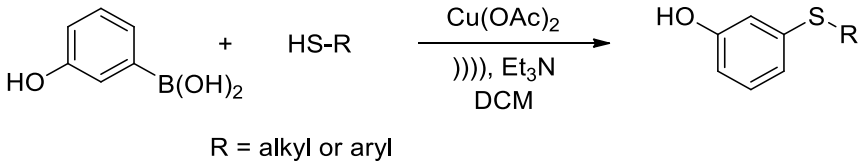
Entry	Starting Material	Product	Yield	Product
1			90	520
2			88	521
3			89	522
4			87	523
5			93	524
6			NR	525
7			88	526

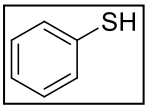
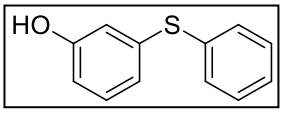
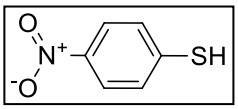
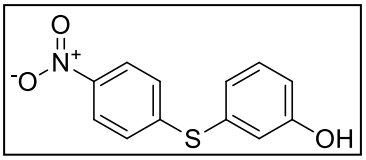
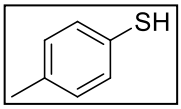
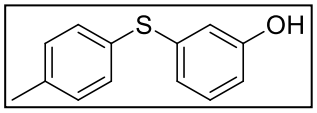
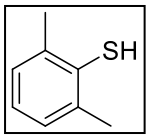
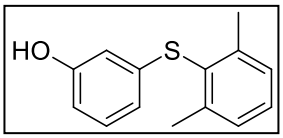
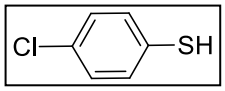
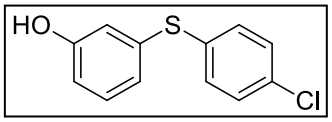
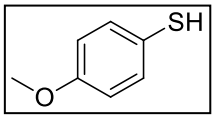
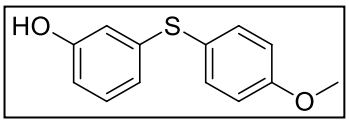
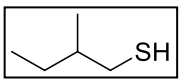
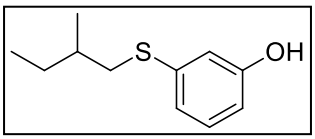
With the exception of the attempted synthesis of 1-(4-((4-methoxyphenyl)thio)phenyl)ethanone, the expected product was formed. There was no homocoupling products were detected, and all unreacted (4-(trifluoromethyl)phenyl)boronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

5.2.4 Reaction of (3-Hydroxyphenyl)boronic Acid with Thiols

Various thiols and thiophenols were mixed with (3-hydroxyphenyl)boronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. The reaction results are presented in **Table 5-4**.

Table 5-4 Reactions of (3-Hydroxyphenyl)boronic Acid with Thiols



Entry	Starting Material	Product	Yield	Product
1			NR	527
2			73	528
3			71	529
4			73	530
5			81	531
6			NR	532
7			96	533

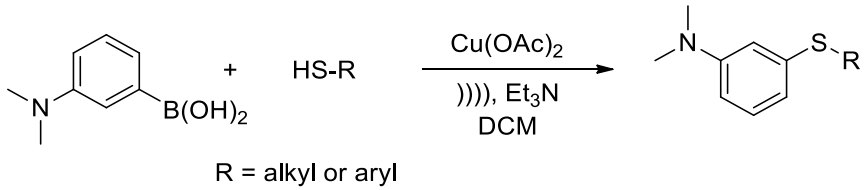
With the exception of the attempted synthesis of 3-(phenylthio)phenol and 3-((4-methoxyphenyl)thio)phenol, the expected product was formed. There was no

homocoupling products were detected, and all unreacted (3-hydroxyphenyl)boronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

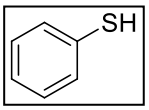
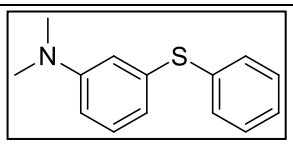
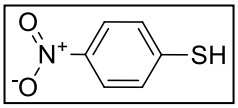
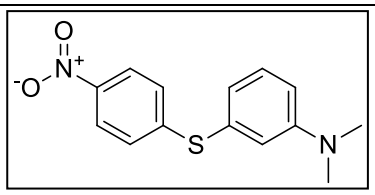
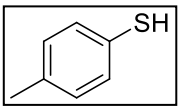
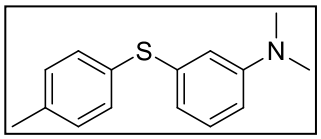
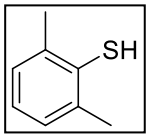
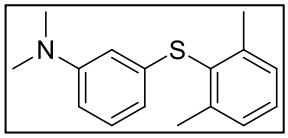
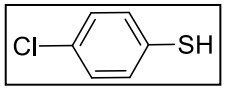
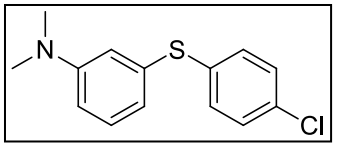
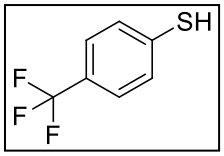
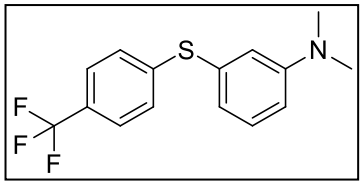
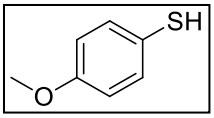
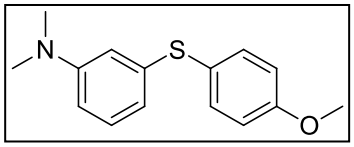
5.2.5 Reaction of (3-(Dimethylamino)phenyl)boronic Acid with Thiols

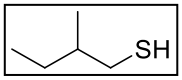
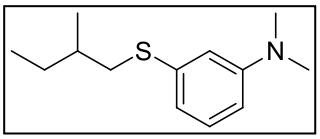
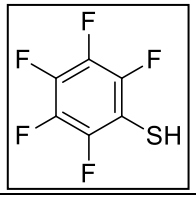
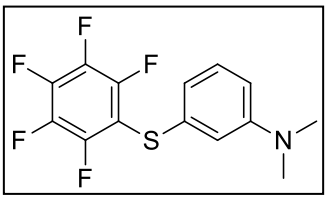
Various thiols and thiophenols were mixed with (3-(dimethylamino)phenyl)boronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. The reaction results are presented in **Table 5-5**.

Table 5-5 Reactions of (3-(Dimethylamino)phenyl)boronic Acid with Thiols



R = alkyl or aryl

Entry	Starting Material	Product	Yield	Product
1			80	534
2			76	535
3			82	536
4			77	537
5			NR	538
6			NR	539
7			NR	540

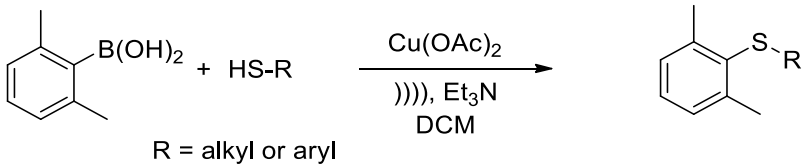
8			98	541
9			NR	542

With the exception of the attempted synthesis of 3-((4-chlorophenyl)thio)-N,N-dimethylaniline, N,N-dimethyl-3-((4-(trifluoromethyl)phenyl)thio)aniline, 3-((4-methoxyphenyl)thio)-N,N-dimethylaniline, and N,N-dimethyl-3-((perfluorophenyl)thio)aniline, the expected product was formed. There was no homocoupling products were detected, and all unreacted (3-(dimethylamino)phenyl)boronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

5.2.6 Reaction of (2,6-Dimethylphenyl)boronic Acid with Thiols

Various thiols were mixed with (2,6-dimethylphenyl)boronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. (**Scheme 5-1**). No products were detected. This was verified with additional experiments. An additional set of experiments were carried out using 6 hours of ultrasonic radiation, again no product formed.

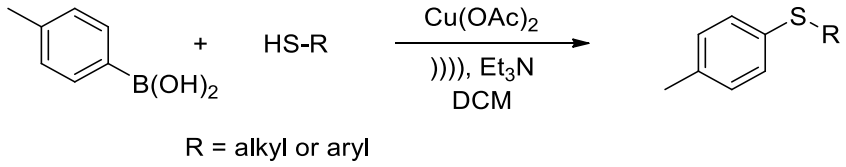
Scheme 5-1 Reaction of (2,6-Dimethylphenyl)boronic Acid with Thiols



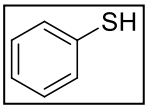
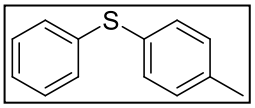
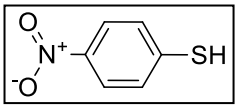
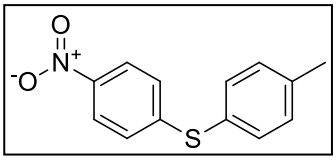
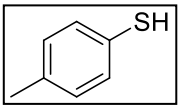
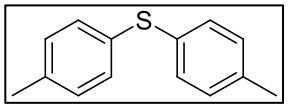
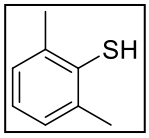
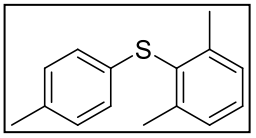
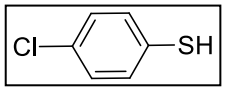
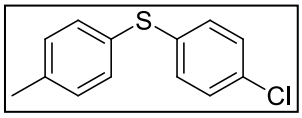
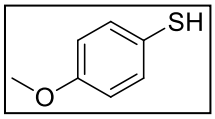
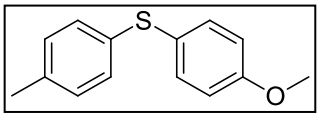
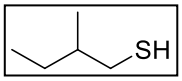
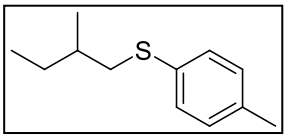
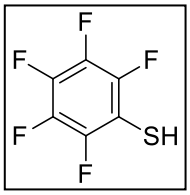
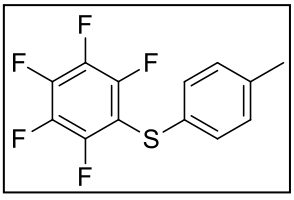
5.2.7 Reaction of p-Tolylboronic Acid with Thiols

Various thiols were mixed with p-tolylboronic acid in DCM, in the presence of copper(II) acetate, and triethylamine. The reaction results are presented in **Table 5-6**.

Table 5-5 Reactions of p-Tolylboronic Acid with Thiols



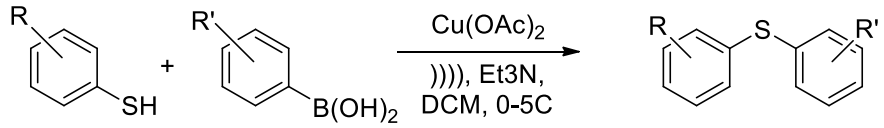
R = alkyl or aryl

Entry	Starting Material	Product	Yield	Product
1			92	543
2			88	544
3			95	545
4			85	546
5			94	547
6			NR	548
7			98	549
8			98	550

With the exception of the attempted synthesis of (4-methoxyphenyl)(p-tolyl)sulfane, the expected product was formed. There was no homocoupling products were detected, and all unreacted (3-(dimethylamino)phenyl)boronic acid remained as the boronic acid. The reactions that showed no product yield had the results verified by additional experiments.

In an attempt to evaluate the electronic effects of the substituent groups on the reaction, the yields were plotted against the reported sigma values, **Table 5-7**:

Table 5-7 Plot of Reactant Sigma Values correlated with Product Yield



R ↓ R' →	meta -OH	meta -NMe2	para -CH3	para -C(O)CH3	para -CF3
para -CH3	71	82	95	89	98
para-OCH3	0	0	0	0	0
H	0	80	92	90	95
para -Cl	81	0	94	93	92
para -CF3		0			0
para -NO2	73	76	88	88	91
2,6 -CH3	73	77	85	87	0
2,3,4,5,6 -F		0	98		94
2-methyl butane-	96	98	98	88	98

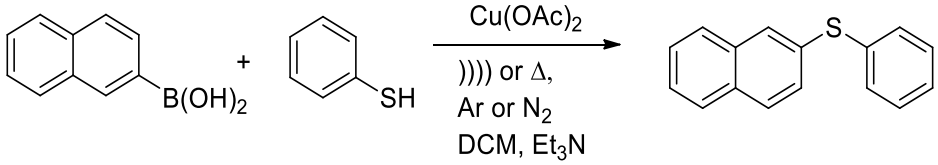
The data indicats that the highest product yields occur when the boronic acid has an electron withdrawing group, while the thiol has a sigma value close to zero.

5.2.8 Mechanistic Study

The method used in this Chapter, parallels that of Chapter 3 (please see Section 3.2.8 for all relevant background information). A series of experiments were conducted, summarized in **Table 5-8**. This series was designed to test for the presence of copper(I)

acetate as well as the possible formation of free radicals. All experiments were conducted as described in Section 2.2.4.

Table 5-8 Summary of Mechanism Investigation Experiments



Entry	Reaction Conditions	Product Yield
1	Naphthylboronic acid, benzenethiol, R.T., 72 hours	61
2	Naphthylboronic acid, benzenethiol, ultrasound 4 hours	92
3	Naphthylboronic acid, benzenethiol, 5eq galvinoxyl R.T., 72 hours	59
4	Naphthylboronic acid, benzenethiol, 5eq galvinoxyl ultrasound 4 hours	91

It is not possible to conduct an ultrasound experiment within an EPR, so to determine if copper(I) acetate is produced, scanning powder-x-ray diffraction was employed. The pXRD analysis revealed that all samples displayed two theta peaks associated with copper(I) acetate post reaction (2θ: 4.3, 7.2, 18, 26.7, 37, 42, 44.8; as compared to the copper(I) standard. The added galvinoxyl had no impact on the reaction product yield. This evidence supports the postulation that ultrasound has no effect on the reaction mechanism.

5.3 Conclusion

The application of ultrasound to the Chan-Lam-Evans modified Ullmann reaction for the S-arylation of various thiols has proven successful. Although the original reaction

does not call for the addition of energy, ultrasound dramatically decreased the reaction time from 72 hours to 4 hours, while improving the product yields (60-100%), and maintaining the mild reaction conditions. The resulting product yields indicates that there is an electronic effect related to the arylboronic acid, which may warrant additional study and further method development. Lam et al. report that S-arylation does not occur in some isolated cases and attributes the lack of reaction to a possible amine base affect.[6b, 7c] With the exception of Section 3.2.6, experiments that did not produce any yields are similar to the reactions reported by Lam.

5.4 Experimental Details

5.4.1 General Considerations

All glassware was dried at 120 °C and flushed with dry nitrogen prior to use. All chemicals were purchased from commercial sources and used as received. Gas Chromatography-Mass Spectroscopy studies were carried out on a Hewlett Packard: HP 6890 series GC System with 5973 Mass Selective Detector; Column: HP-5 30 m x 0.25 mm x 0.25 μm; Gas (He) flow 0.8 ml/min; temperature program: flow 0.8 ml/min, initial temperature 90 °C for 1 minute, a temperature ramp of 15 °/minute up to 200 °C, then a temperature ramp of 5 °/min up to 250 °C for 10 minutes. All samples were purified using column chromatography (anhydrous sodium sulfate and 60 Å 230-400 mesh silica gel), and then recrystallized.

All sonication experiments were carried out using a Fisher Scientific Model 550 Sonic Dismemborator, employing a 0.5 inch horn sonicator and a 1 inch by 2 inch cylindrical reaction vessel. All individual reactions were carried out in new borsite glass

vessels. Reaction vessel external temperature was maintained at 0-5 °C with an ice water bath.

5.4.2 Representative Procedure for the Synthesis of Naphthalen-2-yl(phenyl)sulfane

Naphthylboronic acid (0.25 g, 1.5 mmol) was added to benzenethiol (0.11 g, 1.0 mmol) in 15ml of DCM. Copper(II) acetate (0.36 g, 2.0 mmol) was then added along with triethylamine (0.5g, 5.0 mmol), and the dismemberator horn placed in the reaction vessel. The sonicator was set to 55 watts and the reaction was allowed to proceed for 4 hours (1 minute pulse with a 3 second rest). Post reaction, the product was isolated by column chromatography. Product yields were determined by weight and purity was confirmed by GC/MS and NMR.

5.4.3 Characterization of Compounds 501-550

^{1}H NMR and ^{13}C NMR spectra were recorded either at 250 and 63 MHz or 300 and 75 MHz respectively. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra were referenced to TMS and the d-chloroform solvent shift. High quality mass spectrometry was carried out using a Qstar electron spray ionization mass spectrometer, in either positive (M+1) or negative mode (M-1), ionization energy of ±5000 e/v, injection rate of 20 μl/min.

Naphthalen-2-yl(phenyl)sulfane (501)[53]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 6.1, 3.1 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 4H), 7.26 (dt, *J* = 23.5, 7.1 Hz, 6H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 134.9, 131.4, 127.2, 126.9, 125.8, 125.8, 125.4, 125.2, 125.1,

125.0, 123.8, 123.6. Anal. Calcd for $C_{16}H_{12}S$: 236.0660. Found: 235.0772 (M-1). GC RT 15.85 minutes.

Naphthalen-2-yl(4-nitrophenyl)sulfane (502)[53]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 6.1, 3.3 Hz, 4H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.57 – 7.39 (m, 5H), 7.24 (d, *J* = 6.8 Hz, 1H).). ^{13}C NMR (75 MHz, cdcl$_3$) δ 146.8, 141.9, 135.8, 135.0, 133.7, 130.2, 127.8, 126.3, 125.8, 125.6, 124.4. Anal. Calcd for $C_{16}H_{11}NO_2S$: 281.0510. Found: 280.0447 (M-1). GC RT 9.05 minutes.

Naphthalen-2-yl(p-tolyl)sulfane (503)[53]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.87 (dd, *J* = 6.2, 3.4 Hz, 3H), 7.55 – 7.37 (m, 5H), 7.17 – 7.08 (m, 3H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 140.8, 135.7, 132.1, 131.7, 128.1, 126.8, 126.1, 124.1, 19.3. Anal. Calcd for $C_{17}H_{14}S$: 250.0816. Found: 249.0955 (M-1). GC RT 8.99 minutes.

(2,6-Dimethylphenyl)(naphthalen-2-yl)sulfane (504)[53]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.83 (dd, *J* = 6.2, 3.4 Hz, 1H), 7.46 (dd, *J* = 6.3, 3.3 Hz, 1H), 7.15 – 6.94 (m, 3H), 2.23 (s, 6H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 143.4, 134.7, 133.4, 131.3, 130.8, 129.2, 128.0, 127.8, 127.2, 125.8, 21.4. Anal. Calcd for $C_{18}H_{16}S$: 264.0973. Found: 263.1107 (M-1). GC RT 8.78 minutes.

(4-Chlorophenyl)(naphthalen-2-yl)sulfane (505)[53]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 9.3 Hz, 2H), 7.83 (dt, *J* = 5.8, 2.7 Hz, 3H), 7.38 (dd, *J* = 8.7, 2.2 Hz, 3H), 7.26 (dd, *J* = 8.4, 1.9 Hz, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 135.9, 135.0, 133.6, 133.1, 131.7, 131.1, 129.3, 128.2, 127.8, 127.0, 126.5, 125.8. Anal. Calcd for $C_{16}H_{11}ClS$: 270.0270. Found: 269.0644 (M-1). GC RT 9.94 minutes.

Naphthalen-2-yl(4-(trifluoromethyl)phenyl)sulfane (506)[22]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 8.3 Hz, 2H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.82 (dq, *J* = 5.8, 2.6 Hz, 4H), 7.32 (dd, *J* = 21.9, 8.0 Hz, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 140.8, 134.7, 133.4, 129.7, 127.8, 126.5, 125.8, 125.6, 123.3. Anal. Calcd for $C_{17}H_{11}F_3S$: 304.0534. Found: 303.0728 (M-1). GC RT 11.26 minutes.

(4-Methoxyphenyl)(naphthalen-2-yl)sulfane (507)[54]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 3.4 Hz, 2H), 7.71 (d, *J* = 6.3 Hz, 1H), 7.68 – 7.60 (m, 3H), 7.43 (d, *J* = 3.1 Hz, 2H), 7.41 – 7.33 (m, 3H), 3.74 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 159.6, 133.1, 132.2, 129.0, 128.0, 127.4, 125.4, 114.2, 54.8. Anal. Calcd for $C_{17}H_{14}OS$: 266.0765. Found: 265.1008 (M-1). GC RT 16.14 minutes.

(2-Methylbutyl)(naphthalen-2-yl)sulfane (508)[54]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.77 – 7.57 (m, 3H), 7.47 (s, 1H), 7.28 – 7.13 (m, 3H), 2.73 (dd, *J* = 12.7, 5.8 Hz, 2H), 2.54 (dd, *J* = 12.8, 7.5 Hz, 2H), 1.79 – 1.66 (m, 1H), 1.56 – 1.42 (m, 2H), 1.03 – 0.85 (m, 6H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 130.5, 129.7, 129.2, 128.3, 127.5, 126.0, 125.9, 44.8, 34.4, 28.4, 23.3, 11.2. Anal. Calcd for $C_{15}H_{18}S$: 230.1129. Found: 229.0918 (M-1). GC RT 12.99 minutes.

Naphthalen-2-yl(perfluorophenyl)sulfane (509)[22]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.82 (d, *J* = 3.4 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.60 – 7.44 (m, 3H), 7.36 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (63 MHz, D_2O) δ 150.0, 141.9, 138.4, 133.5, 129.7, 129.1, 128.6, 126.9, 126.7, 125.7, 100.3. Anal. Calcd for $C_{16}H_7F_5S$: 326.0189. Found: 325.0344 (M-1). GC RT 15.64 minutes.

Phenyl(4-(trifluoromethyl)phenyl)sulfane (511)[53]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.53 (d, *J* = 7.4 Hz, 2H), 7.28 (dt, *J* = 23.6, 7.1 Hz, 6H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 139.5, 137.0, 129.0, 127.5, 127.1, 126.7, 126.7, 124.6, 122.8. Anal. Calcd for $C_{13}H_9F_3S$: 254.0377. Found: 253.0475 (M-1). GC RT 13.75 minutes.

(4-Nitrophenyl)(4-(trifluoromethyl)phenyl)sulfane (512)[53]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 17.5 Hz, 2H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 149.63, 141.64, 139.66, 132.68, 129.21, 126.08, 124.53, 123.95. Anal. Calcd for $C_{13}H_8F_3NO_2S$: 299.0228. Found: 298.0500 (M-1). GC RT 12.37 minutes.

p-Tolyl(4-(trifluoromethyl)phenyl)sulfane (513)[55]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 – 7.39 (m, 4H), 7.18 – 7.09 (m, 4H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 138.1, 137.4, 130.2, 129.7, 128.6, 123.3, 119.8, 20.9. Anal. Calcd for $C_{14}H_{11}F_3S$: 268.0534. Found: 127.0784 (M-1). GC RT 12.11minutes.

(4-Chlorophenyl)(4-(trifluoromethyl)phenyl)sulfane (515)[55]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.84 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 17.5 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 143.0, 135.1, 133.6, 131.7, 131.1, 129.3, 127.8, 125.8. Anal. Calcd for $C_{13}H_8ClF_3S$: 287.9987. Found: 287.0002 (M-1). GC RT 9.42 minutes.

(2-Methylbutyl)(4-(trifluoromethyl)phenyl)sulfane (518)[22]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.35-7.29 (m, 4H), 2.73 (dd, *J* = 12.7, 5.8 Hz, 2H), 2.54 (dd, *J* = 12.8, 7.5 Hz, 2H), 1.80 – 1.64 (m, 1H), 1.57 – 1.41 (m, 2H), 1.04 – 0.84 (m, 6H). ^{13}C

NMR (63 MHz, D_2O) δ 142.5, 131.6, 128.5, 127.8, 125.8, 46.7, 34.5, 28.5, 18.6, 11.2. Anal. Calcd for $C_{12}H_{15}F_3S$: 248.0847. Found: 247.0747 (M-1). GC RT 6.96 minutes.

(Perfluorophenyl)(4-(trifluoromethyl)phenyl)sulfane (519)[20b]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.50 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (63 MHz, D_2O) δ 149.0, 141.0, 138.2, 135.9, 133.3, 132.4, 129.0, 126.3, 100.6. Anal. Calcd for $C_{13}H_4F_8S$: 343.9906. Found: 343.0001 (M-1). GC RT 7.34 minutes.

1-(4-(Phenylthio)phenyl)ethanone (520)[53]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.91 (d, *J* = 5.8 Hz, 2H), 7.60 (d, *J* = 12.6 Hz, 2H), 7.45 (d, *J* = 6.8 Hz, 2H), 7.21 (dd, *J* = 13.1, 6.5 Hz, 3H), 2.55 (s, 3H). ^{13}C NMR (63 MHz, D_2O) δ 197.5, 143.0, 134.6, 133.1, 128.8, 128.0, 127.8, 126.7, 26.1. Anal. Calcd for $C_{14}H_{12}OS$: 228.0609. Found: 227.0889 (M-1). GC RT 17.60 minutes.

1-(4-((4-Nitrophenyl)thio)phenyl)ethanone (521)[16e]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 8.3 Hz, 2H), 7.96 (d, *J* = 7.4 Hz, 2H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 2.61 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 196.7, 146.9, 144.0, 141.9, 133.1, 129.5, 128.3, 124.4, 26.6. Anal. Calcd for $C_{14}H_{11}NO_3S$: 273.0460. Found: 272.0551 (M-1). GC RT 12.50 minutes.

1-(4-(p-Tolylthio)phenyl)ethanone (522)[22]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.97 (d, *J* = 7.9 Hz, 2H), 7.26 (dd, *J* = 75.5, 7.5 Hz, 4H), 6.78 (d, *J* = 8.4 Hz, 2H), 2.60 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (63 MHz, D_2O) δ 193.0, 137.6, 134.1, 129.7, 129.7, 128.4, 128.4, 30.6, 20.9. Anal. Calcd for $C_{15}H_{14}OS$: 242.0765. Found: 241.0510 (M-1). GC RT 13.63 minutes.

1-(4-((2,6-Dimethylphenyl)thio)phenyl)ethanone (523)[22]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.96 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.52 – 7.42 (m, 2H), 7.10 (dd, *J* = 8.3, 6.6 Hz, 1H), 2.60 (s, 3H), 2.23 (s, 9H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 198.1, 143.3, 137.1, 134.7, 129.2, 128.5, 128.0, 127.6, 126.9, 77.4, 77.0, 76.6, 26.6, 21.4. Anal. Calcd for $C_{16}H_{16}OS$: 256.0922. Found: 255.1002 (M-1). GC RT 12.27 minutes.

1-(4-((4-Chlorophenyl)thio)phenyl)ethanone (524)[53]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.95 (d, *J* = 7.3 Hz, 2H), 7.43 (dd, *J* = 23.0, 8.1 Hz, 4H), 6.82 (d, *J* = 8.4 Hz, 2H), 2.60 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 196.6, 144.0, 133.1, 132.6, 131.4, 129.9, 128.5, 128.3, 26.6. Anal. Calcd for $C_{14}H_{11}ClOS$: 262.0219. Found: 261.0442 (M-1). GC RT 9.46 minutes.

1-(4-((2-Methylbutyl)thio)phenyl)ethanone (526)[7a]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.30-7.22 (m, 4H), 2.77 (dd, *J* = 12.7, 5.8 Hz, 2H), 2.58 (dd, *J* = 12.8, 7.5 Hz, 2H), 2.50 (s, 3H), 1.76 – 1.68 (m, 1H), 1.55 – 1.50 (m, 2H), 1.00 – 0.88 (m, 6H). ^{13}C NMR (63 MHz, D_2O) δ 193.5, 137.1, 133.4, 130.4, 123.5, 46.7, 34.5, 28.5, 18.6, 11.2. Anal. Calcd for $C_{13}H_{18}OS$: 222.1078. Found: 221.0887 (M-1). GC RT 6.96 minutes.

3-((4-Nitrophenyl)thio)phenol (528)[54]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 8.15 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 7.17 (s, 1H), 6.85 (dd, *J* = 25.1, 7.5 Hz, 3H), 5.02 (s, 1H). ^{13}C NMR (63 MHz, D_2O) δ 158.4, 144.0, 140.4, 137.0, 129.6, 124.4, 118.7, 115.2. Anal. Calcd for $C_{12}H_9NO_3S$: 247.0303. Found: 246.0541 (M-1). GC RT 6.15 minutes.

3-(p-Tolylthio)phenol (529)[45]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.37 (d, *J* = 7.9 Hz, 2H), 7.13 (dd, *J* = 28.6, 7.7 Hz, 4H), 6.93 – 6.65 (m, 2H), 5.23 (s, 1H), 2.29 (s, 3H).

^{13}C NMR (63 MHz, D_2O) δ 158.9, 140.4, 137.3, 133.8, 130.0, 129.7, 129.7, 128.4, 120.1, 115.24, 113.0, 20.9. Anal. Calcd for $C_{13}H_{12}OS$: 216.0609. Found: 215.0887 (M-1). GC RT 11.62 minutes.

3-((2,6-Dimethylphenyl)thio)phenol (530)[45]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.24 (d, *J* = 7.5 Hz, 2H), 7.18 – 6.97 (m, 4H), 6.94 (t, *J* = 7.0 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 2H), 5.30 (s, 1H), 2.25 (s, 6H). ^{13}C NMR (75 MHz, $cdcl_3$) δ 155.5, 143.4, 134.7, 129.6, 129.3, 128.0, 123.1, 120.7, 115.2, 21.4. Anal. Calcd for $C_{14}H_{14}OS$: 230.0765. Found: 229.0455 (M-1). GC RT 12.45 minutes.

3-((4-Chlorophenyl)thio)phenol (531)[53]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.91 – 6.79 (m, 2H), 6.62 – 6.42 (m, 2H), 5.25 (s, 1H). ^{13}C NMR (63 MHz, D_2O) δ 158.7, 135.1, 133.6, 129.5, 129.3, 126.3, 119.9, 115.3. Anal. Calcd for $C_{12}H_9ClOS$: 236.0063. Found: 235.0150 (M-1). GC RT 9.48 minutes.

3-((2-Methylbutyl)thio)phenol (533)[7a]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.28-6.83 (m, 4H), 5.57 (s, 1H), 2.70 (dd, *J* = 12.7, 5.8 Hz, 2H), 2.54 (dd, *J* = 12.8, 7.5 Hz, 2H), 1.75 – 1.69 (m, 1H), 1.52 – 1.45 (m, 2H), 0.99 – 0.88 (m, 6H). ^{13}C NMR (63 MHz, D_2O) δ 158.1, 138.3, 129.5, 120.3, 116.3, 115.3, 46.6, 34.4, 28.4, 18.5, 11.2. Anal. Calcd for $C_{11}H_{16}OS$: 196.0922. Found: 195.0504 (M-1). GC RT 6.98 minutes.

N,N-Dimethyl-3-(phenylthio)aniline (534)[7a]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.49 (t, *J* = 7.6 Hz, 3H), 7.24 (dt, *J* = 23.3, 6.9 Hz, 4H), 6.68 (dd, *J* = 8.6 Hz, 2H), 2.91 (s, 6H). ^{13}C NMR (75 MHz, $cdcl_3$) δ 151.0, 137.7, 137.0, 129.0, 127.5, 127.1, 121.2,

116.9, 112.6, 42.5. Anal. Calcd for $C_{14}H_{15}NS$: 229.0925. Found: 228.0645 (M-1). GC RT 14.67 minutes.

N,N-Dimethyl-3-((4-nitrophenyl)thio)aniline (535)[20b]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.26 (s, 1H), 7.13 (t, *J* = 1.3 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 9.5 Hz, 2H), 2.94 (s, 3H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 151.7, 144.1, 141.3, 138.3, 131.4, 129.1, 124.5, 122.6, 118.0, 112.7, 40.6. Anal. Calcd for $C_{14}H_{14}N_2O_2S$: 274.0776. Found: 273.1141 (M-1). GC RT 6.02 minutes.

N,N-Dimethyl-3-(p-tolylthio)aniline (536)[53]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.37 (d, *J* = 7.8 Hz, 2H), 7.30 (s, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 2H), 6.95 – 6.67 (m, 2H), 3.08 (s, 6H), 2.29 (s, 3H). ^{13}C NMR (63 MHz, D_2O) δ 150.5, 141.7, 137.3, 133.8, 129.7, 129.0, 128.4, 122.7, 116.5, 112.6, 40.5, 21.0. Anal. Calcd for $C_{15}H_{17}NS$: 243.1082. Found: 242.0778 (M-1). GC RT 21.96 minutes.

3-((2,6-Dimethylphenyl)thio)-N,N-dimethylaniline (537)[56]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 (s, 1H), 7.25 (d, *J* = 7.0 Hz, 2H), 7.10-7.01 (m, 5H), 6.75-6.55 (dd, *J* = 7.0 Hz, 4H), 2.94 (s, 9H), 2.23 (s, 9H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 150.6, 143.4, 138.6, 130.8, 129.2, 128.0, 127.0, 121.3, 116.6, 112.6, 40.6, 21.4. Anal. Calcd for $C_{16}H_{19}NS$: 257.1238. Found: 256.0998 (M-1). GC RT 9.78 minutes.

N,N-Dimethyl-3-((2-methylbutyl)thio)aniline (541)[20b]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.28 – 7.27 (m, 2H), 7.06 – 6.81 (m, 2H), 2.99 (s, 6H), 2.63 (ddd, *J* = 59.8, 12.8, 6.7 Hz, 2H), 1.72 (dq, *J* = 13.3, 6.6 Hz, 1H), 1.57 – 1.39 (m, 2H), 1.02 – 0.86 (m, 6H). ^{13}C NMR (75 MHz, cdcl$_3$) δ 152.1, 138.4, 128.4, 116.2, 111.2, 109.8, 46.6,

40.9, 34.4, 28.4, 18.5, 11.1. Anal. Calcd for $C_{13}H_{21}NS$: 223.1395. Found: 222.1012 (M-1). GC RT 9.79 minutes.

Phenyl(p-tolyl)sulfane (543)[53]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.51 – 7.44 (m, 4H), 7.30 – 7.16 (m, 3H), 6.99 (d, *J* = 8.9 Hz, 2H), 2.23 (s, 3H). ^{13}C NMR (63 MHz, D_2O) δ 140.4, 137.0, 129.0, 128.1, 127.5, 127.1, 23.3. Anal. Calcd for $C_{13}H_{12}S$: 200.0660. Found: 199.0881 (M-1). GC RT 13.49 minutes.

(4-Nitrophenyl)(p-tolyl)sulfane (544)[19b]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.18 (dd, *J* = 8.8 Hz, 4H), 7.61 (dd, *J* = 8.8 Hz, 4H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $cdcl_3$) δ 144.1, 140.2, 137.4, 132.3, 129.6, 127.9, 124.4, 21.5. Anal. Calcd for $C_{13}H_{11}NO_2S$: 245.0510. Found: 244.0781 (M-1). GC RT 9.21 minutes.

di-p-Tolylsulfane (545)[53]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 (d, *J* = 8.1 Hz, 4H), 7.11 (d, *J* = 7.9 Hz, 4H), 2.33 (s, 6H). ^{13}C NMR (63 MHz, D_2O) δ 137.4, 130.5, 129.8, 128.5, 21.0. Anal. Calcd for $C_{14}H_{14}S$: 214.0816. Found: 213.0664 (M-1). GC RT 14.06 minutes.

(2,6-Dimethylphenyl)(p-tolyl)sulfane (546)[53]: ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.6, 1.1 Hz, 2H), 7.18 – 6.97 (m, 5H), 2.25 (s, 9H). ^{13}C NMR (75 MHz, $cdcl_3$) δ 142.9, 139.0, 134.2, 129.5, 128.8, 128.3, 127.6, 127.3, 21.4, 21.0. Anal. Calcd for $C_{15}H_{16}S$: 228.0973. Found: 227.1221 (M-1). GC RT 5.26 minutes.

(4-Chlorophenyl)(p-tolyl)sulfane (547)[7a]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.77 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 7.0 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (63 MHz, D_2O) δ 140.6, 135.0, 133.5, 129.8, 129.2,

129.1, 20.4. Anal. Calcd for $C_{13}H_{11}ClS$: 234.0270. Found: 233.0478 (M-1). GC RT 5.26 minutes.

(2-Methylbutyl)(p-tolyl)sulfane (549)[22]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.22 (d, *J* = 4.8 Hz, 1H), 7.14 (d, *J* = 2.3 Hz, 1H), 2.59 (ddd, *J* = 50.5, 12.8, 6.7 Hz, 40H), 2.31 (s, 1H), 1.68 (dq, *J* = 13.3, 6.5 Hz, 26H), 1.43 (dt, *J* = 12.7, 7.1 Hz, 21H), 1.02 – 0.81 (m, 108H). ^{13}C NMR (63 MHz, D_2O) δ 136.5, 132.6, 129.8, 128.9, 46.6, 34.4, 28.5, 20.4, 18.5, 11.2. Anal. Calcd for $C_{12}H_{18}S$: 194.1129. Found: 193.0889 (M-1). GC RT 6.95 minutes.

(Perfluorophenyl)(p-tolyl)sulfane (550)[19b]: ^{1}H NMR (250 MHz, Deuterium Oxide) δ 7.27 (d, *J* = 7.3 Hz, 2H), 7.08 (d, *J* = 7.0 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (63 MHz, D_2O) δ 150.6, 141.7, 140.0, 136.0, 133.7, 131.5, 130.2, 102.2, 24.8. Anal. Calcd for $C_{13}H_7F_5S$: 290.0189. Found: 289.0471 (M-1). GC RT 8.60 minutes.

CONCLUSION

The dissertation contains a description of new methods that were developed for aryl homocoupling and aryl-heteroatom coupling. The method for homocoupling of various aryl compounds employed the use of Dowex polymer support. This allowed the reaction to be carried out in aqueous ethanol instead of an organic solvent, providing a "green" synthesis method. The use of high intensity ultrasound resulted in decreased reaction times and metal catalyst loading while improving product yields – as compared to the traditional Ullmann reaction. The use of copper(II) acetate, instead of palladium, allows the reaction to be conducted at a lower cost than the Suzuki reaction.

The second method initially employed the same polymer based support in aryl-heteroatom coupling reactions. Unfortunately this was not successful, however it did lead to an improvement of the Chan-Lam-Evans modified Ullmann reaction. The application of ultrasound to the reaction dramatically decreased the reaction time from 72 hours to 4 hours while improving the product yields an average of 20% over those reported in the literature.

The methods were successfully scaled from the millimole level to gram level while maintaining good product yields. Both methods use copper(II) acetate as a metal co-reactant, with mechanism studies revealing that the metal undergoes an oxidation / reduction transformation. The new coupling methodology can be characterized as atom efficient, scalable, environmentally friendly, inexpensive, and capable of rapidly producing high yields of products.

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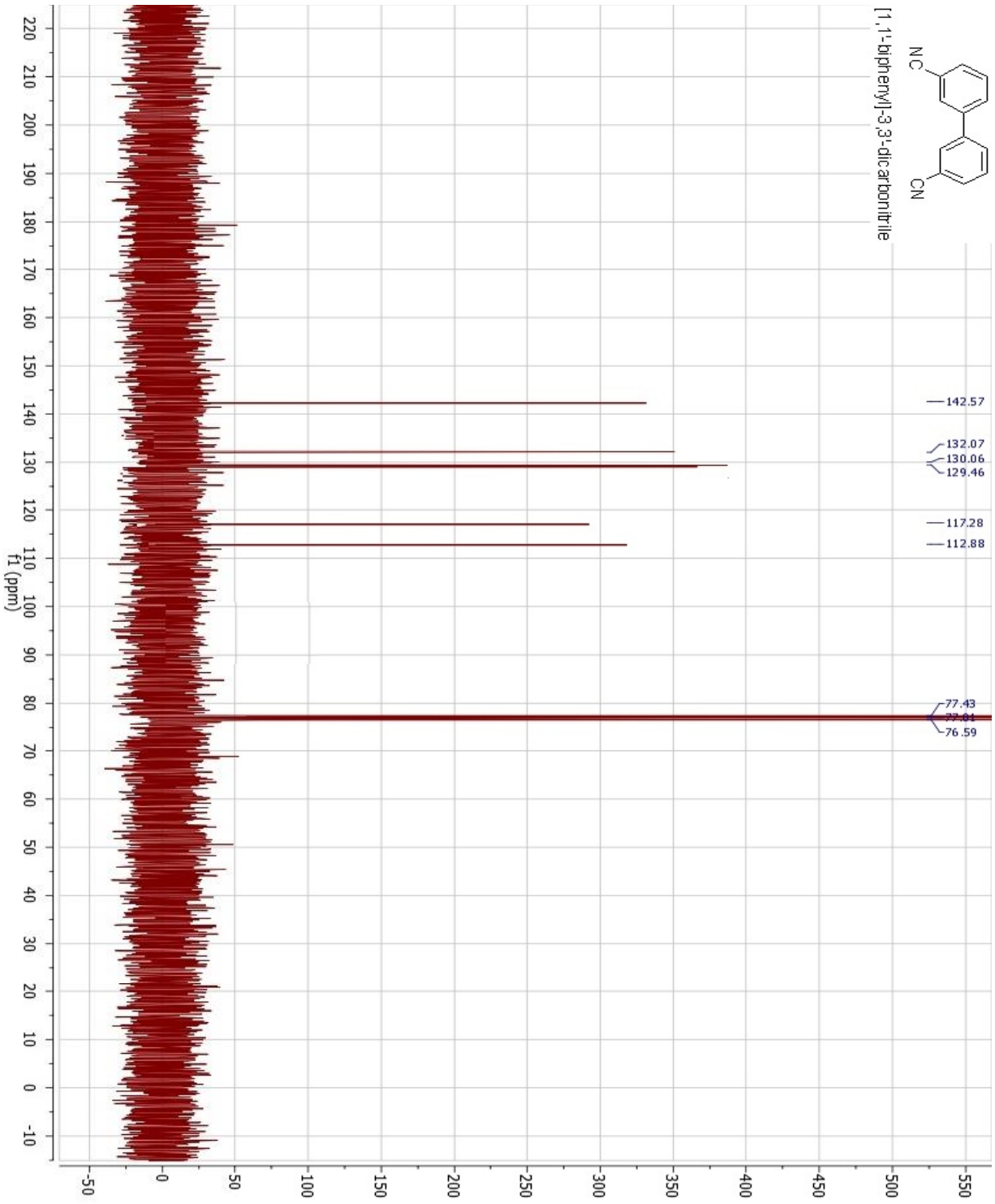
APPENDIX

A. NMR SPECTRA

^{13}Carbon NMR



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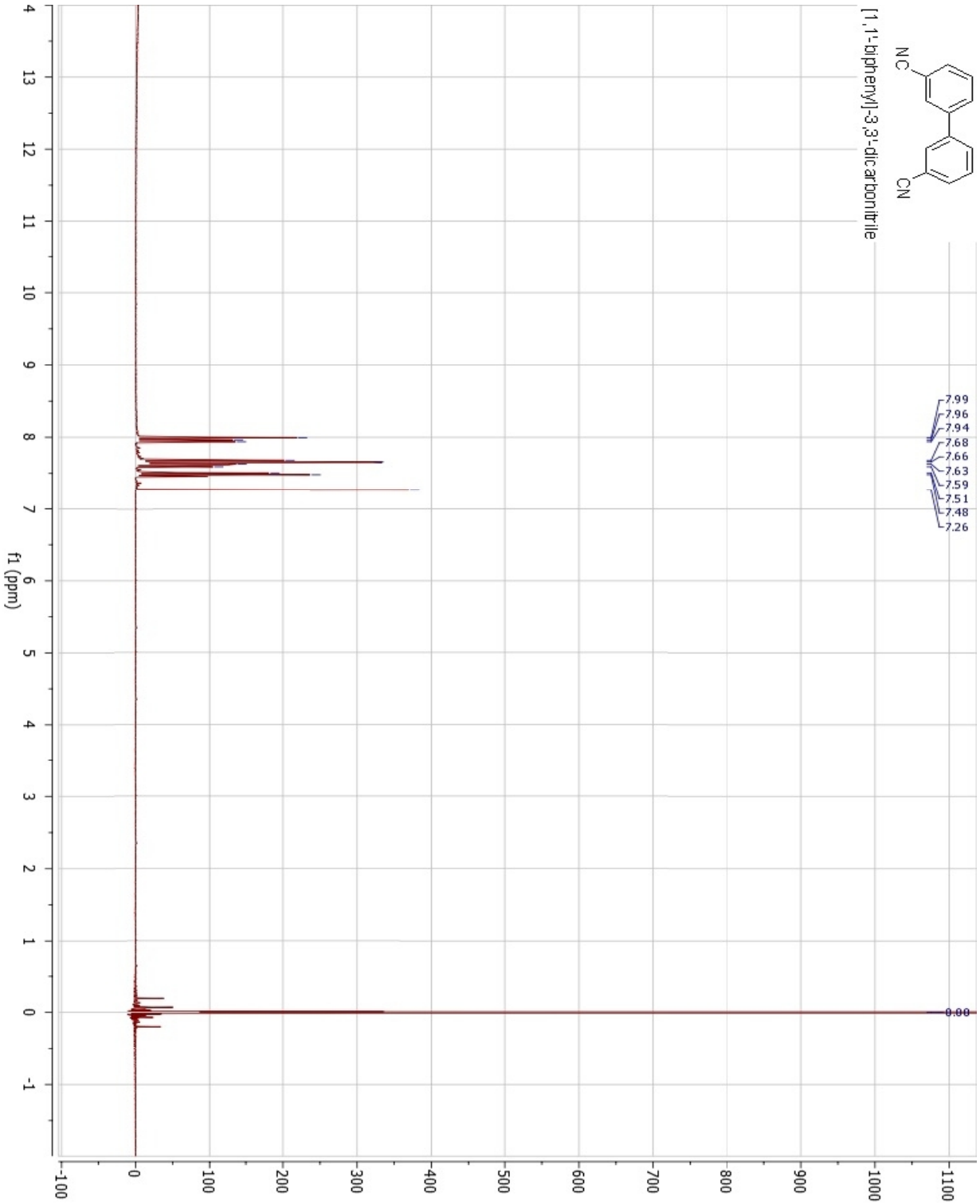

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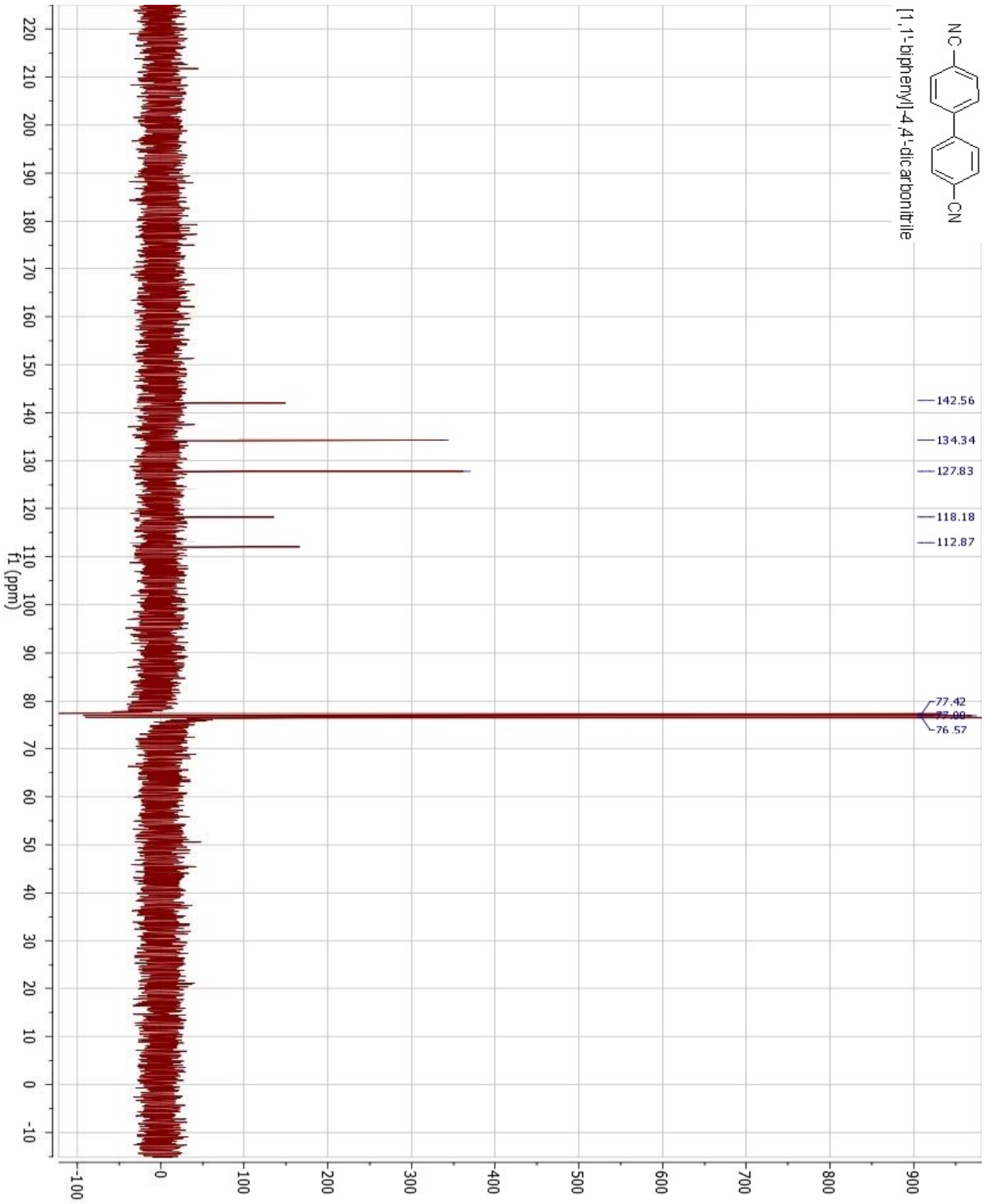

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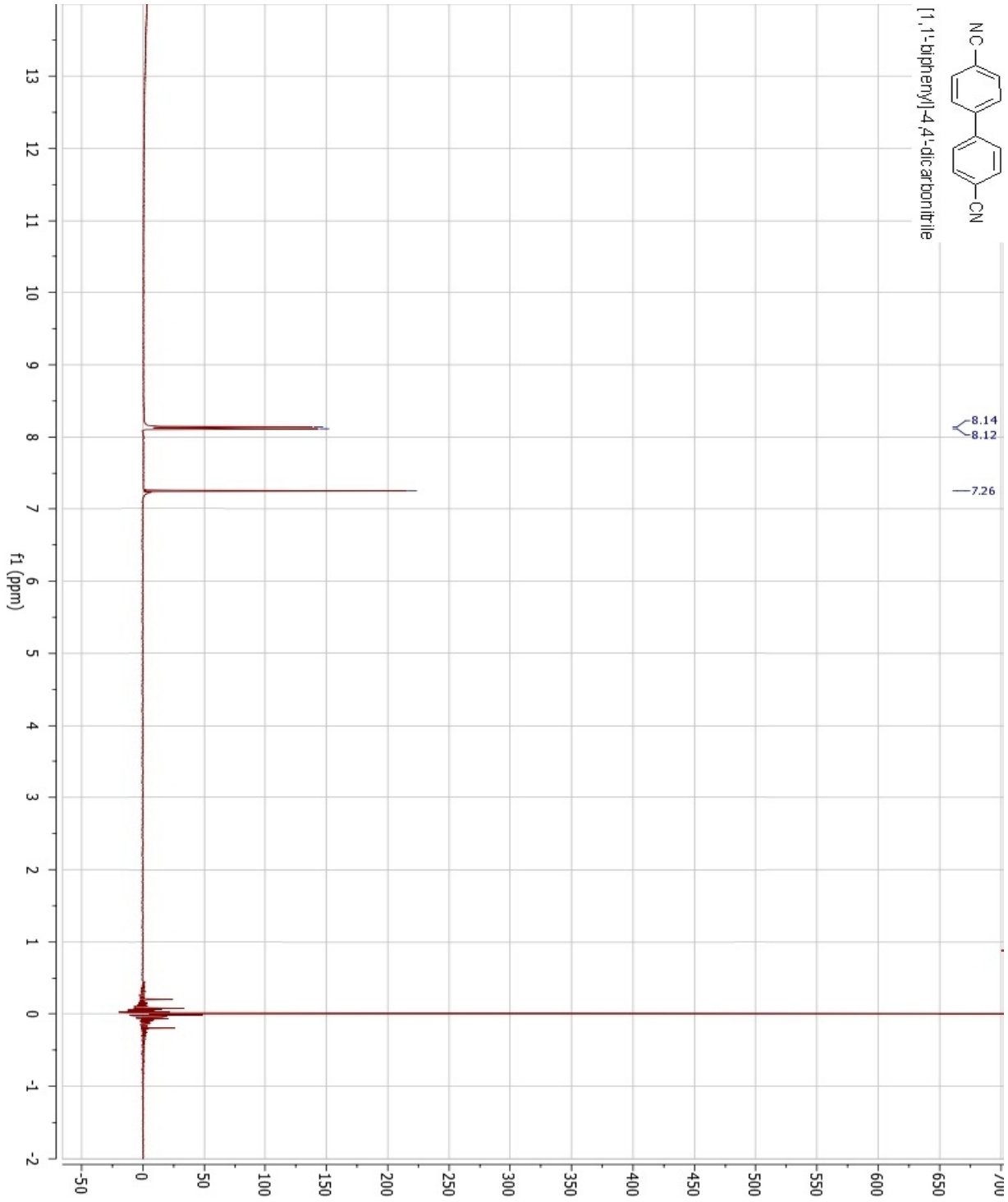

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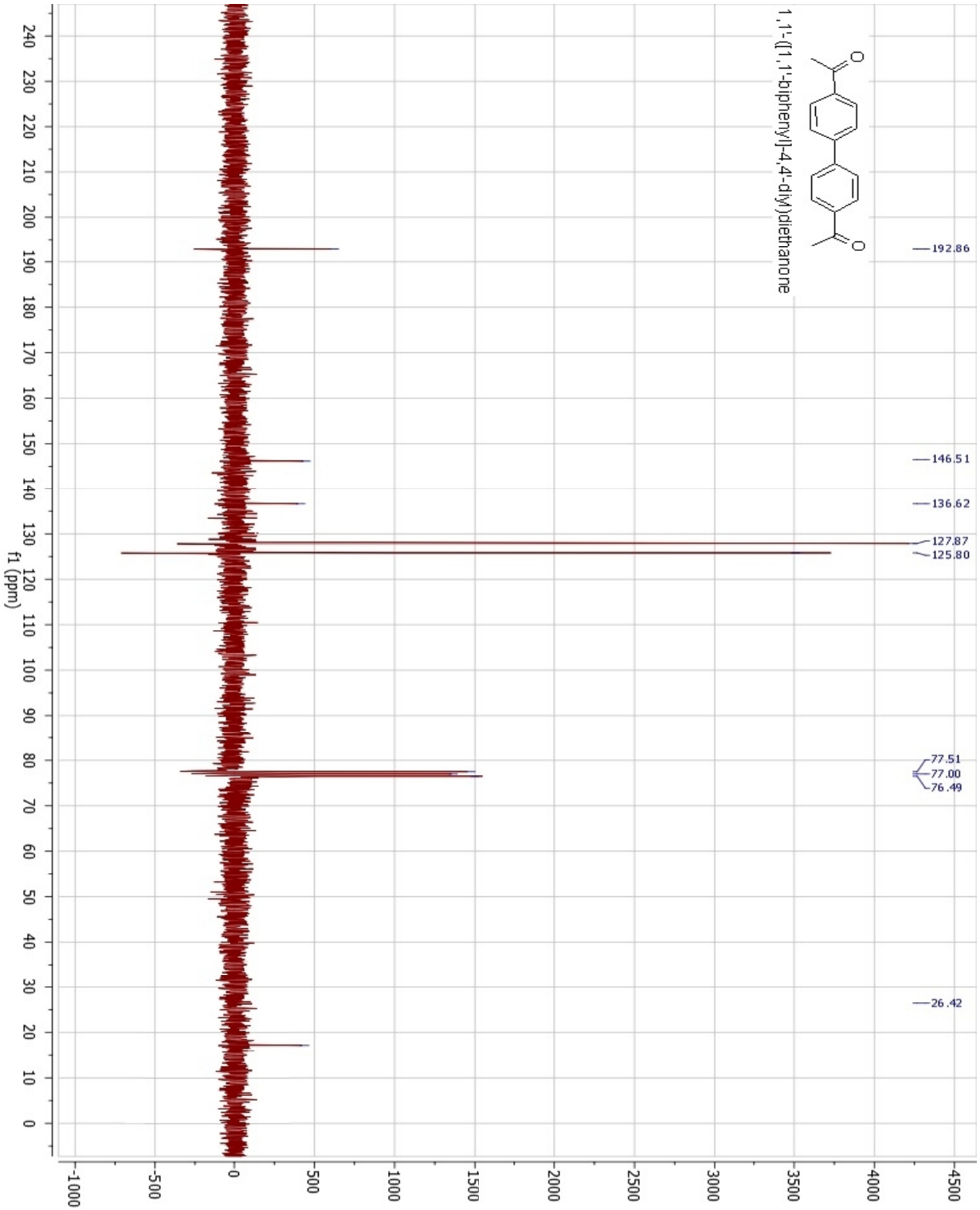

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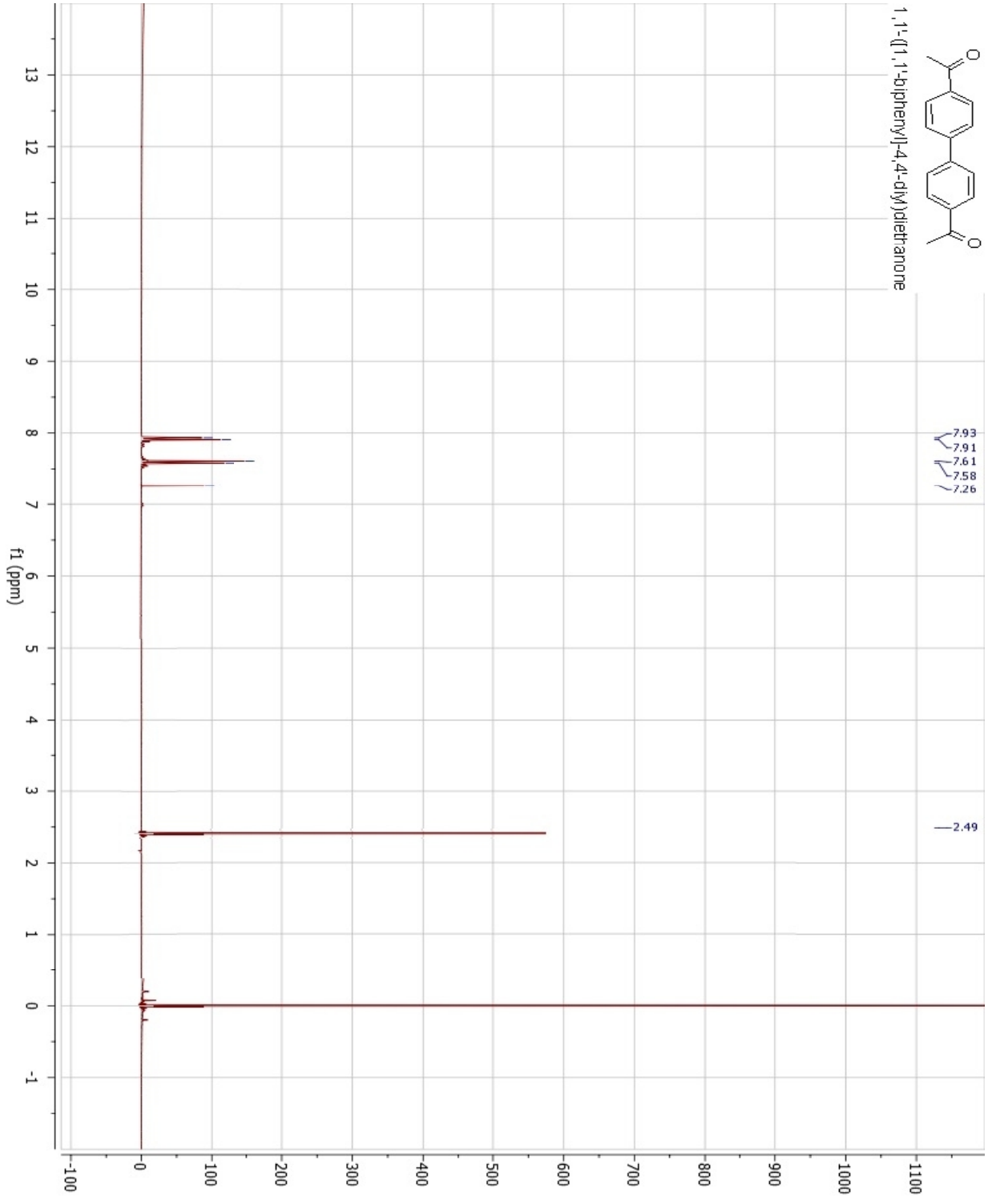

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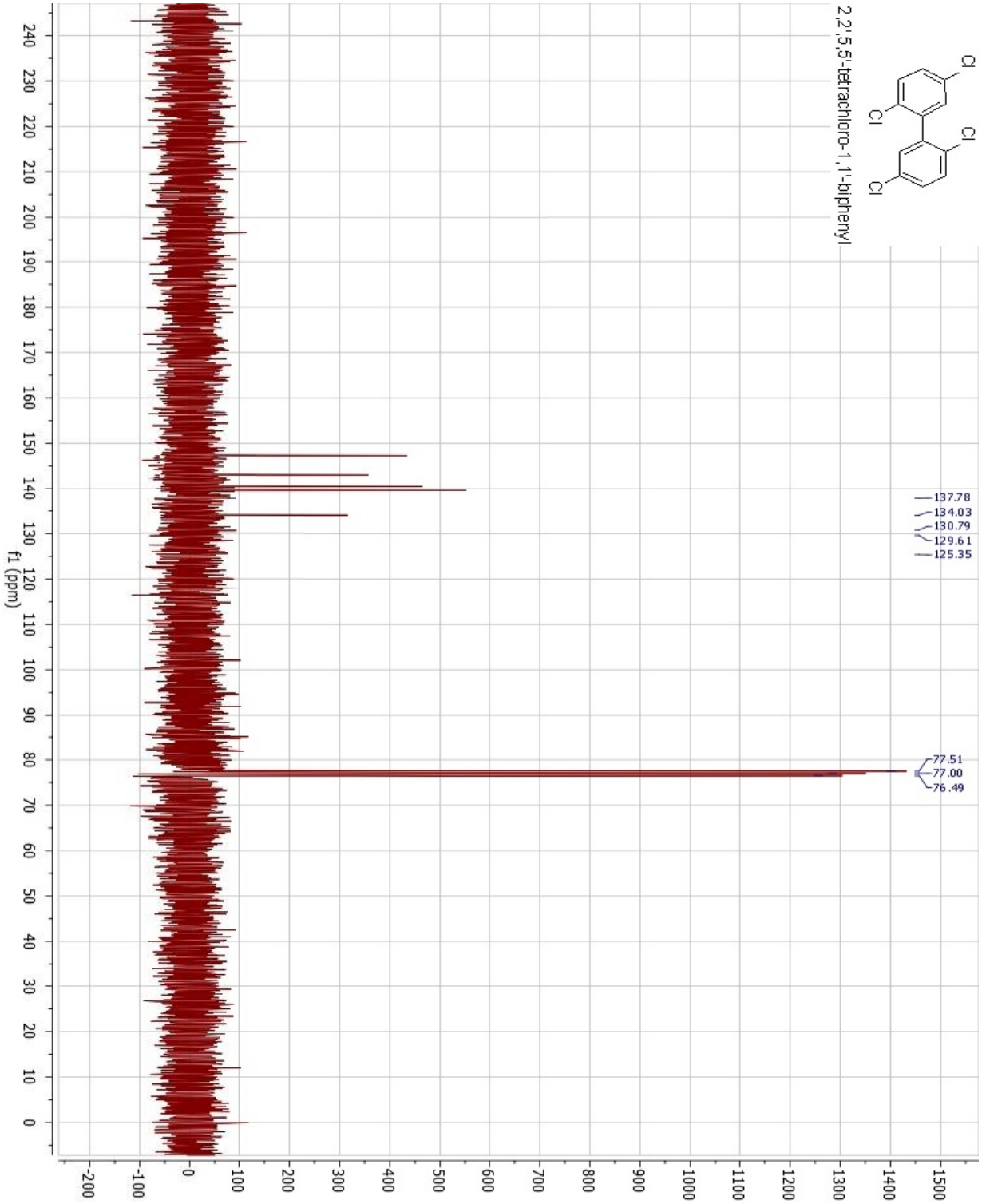

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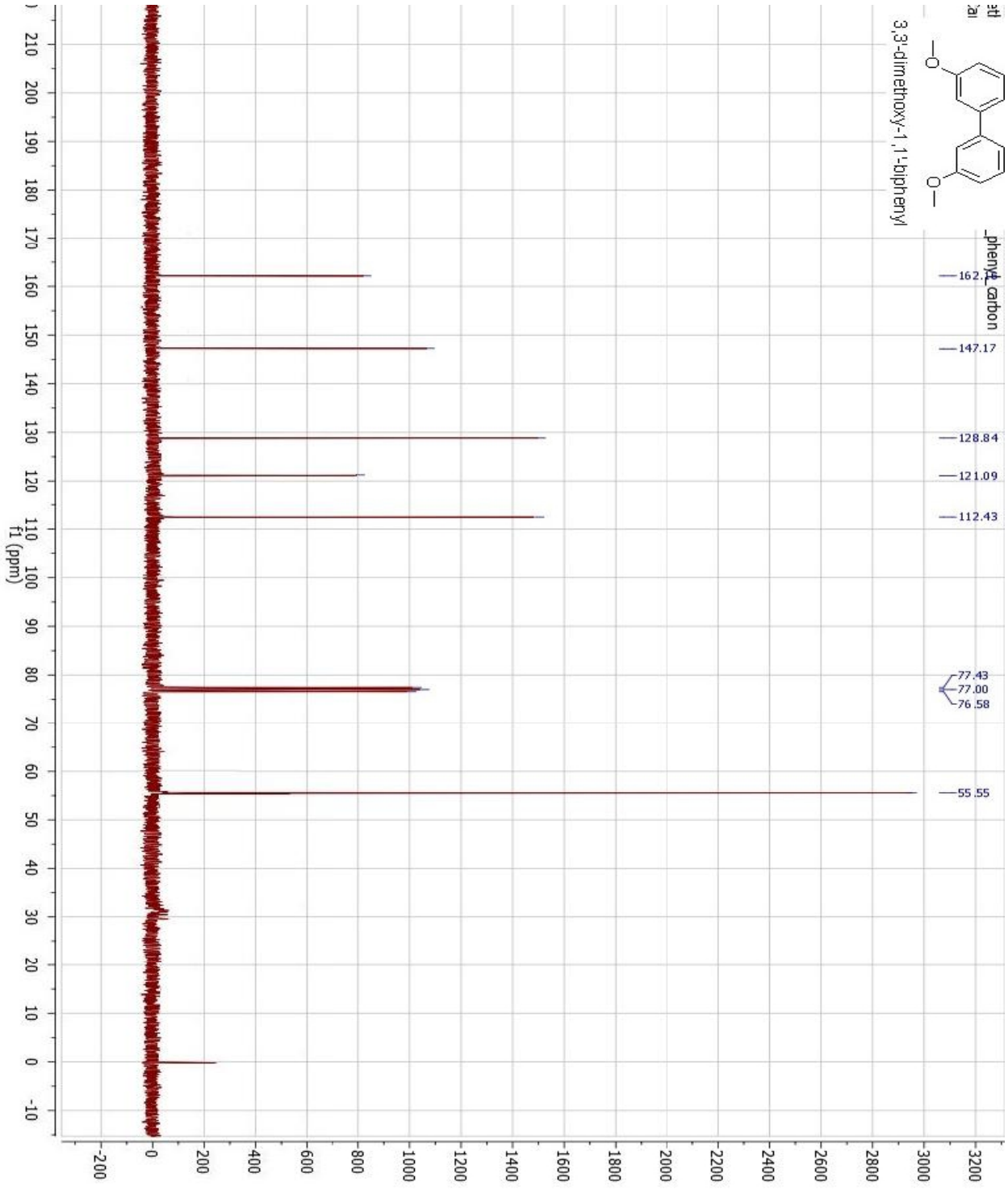

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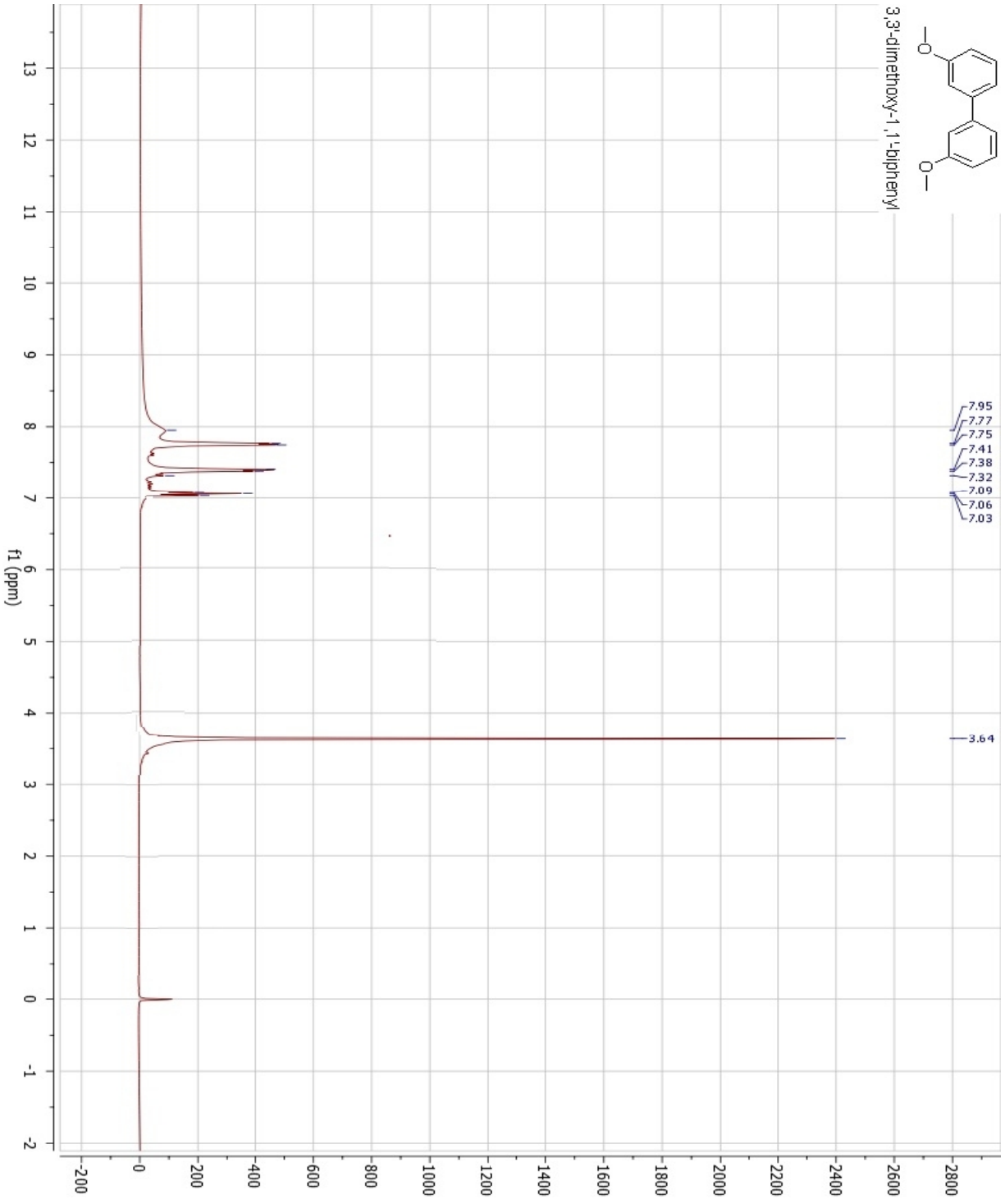

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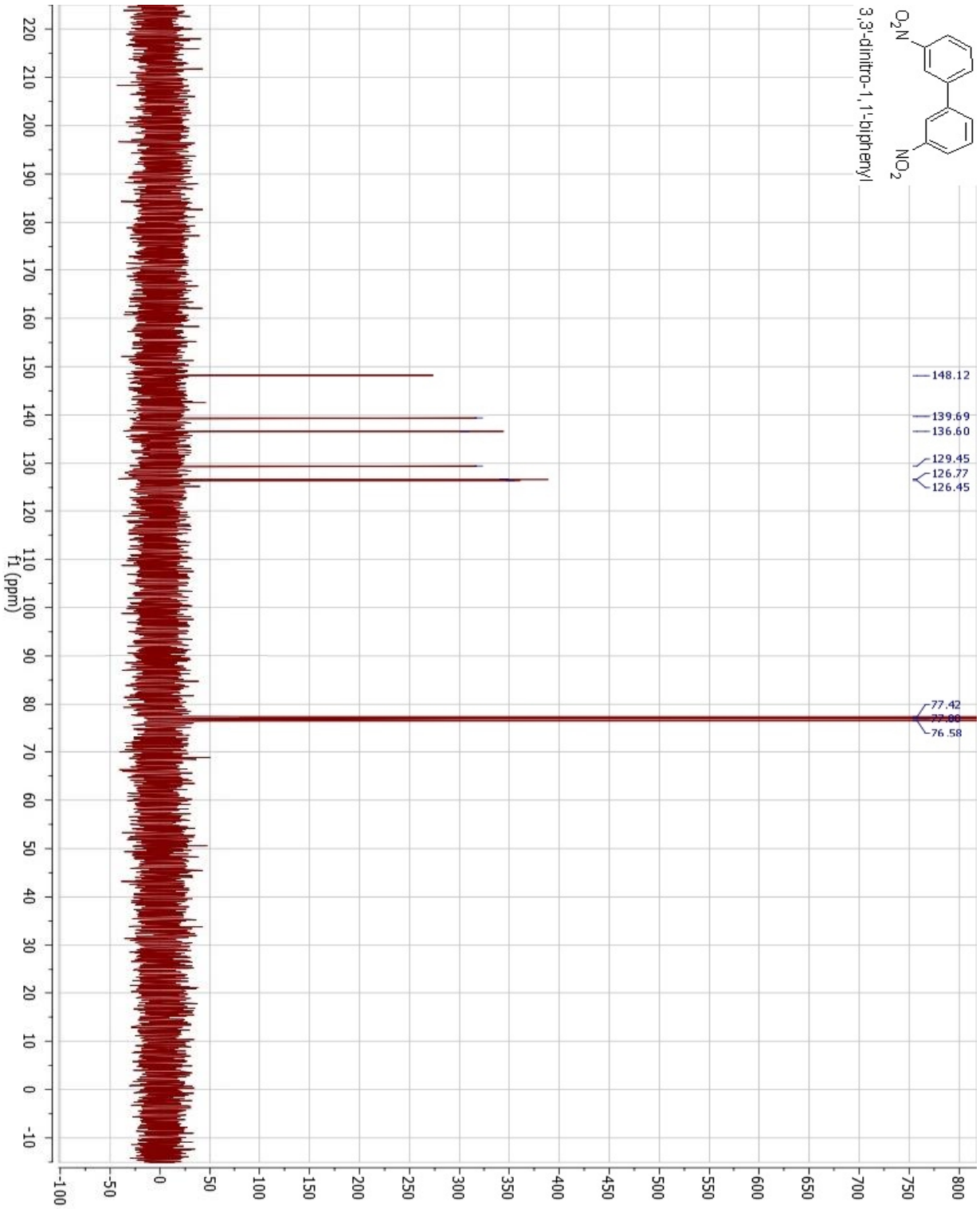

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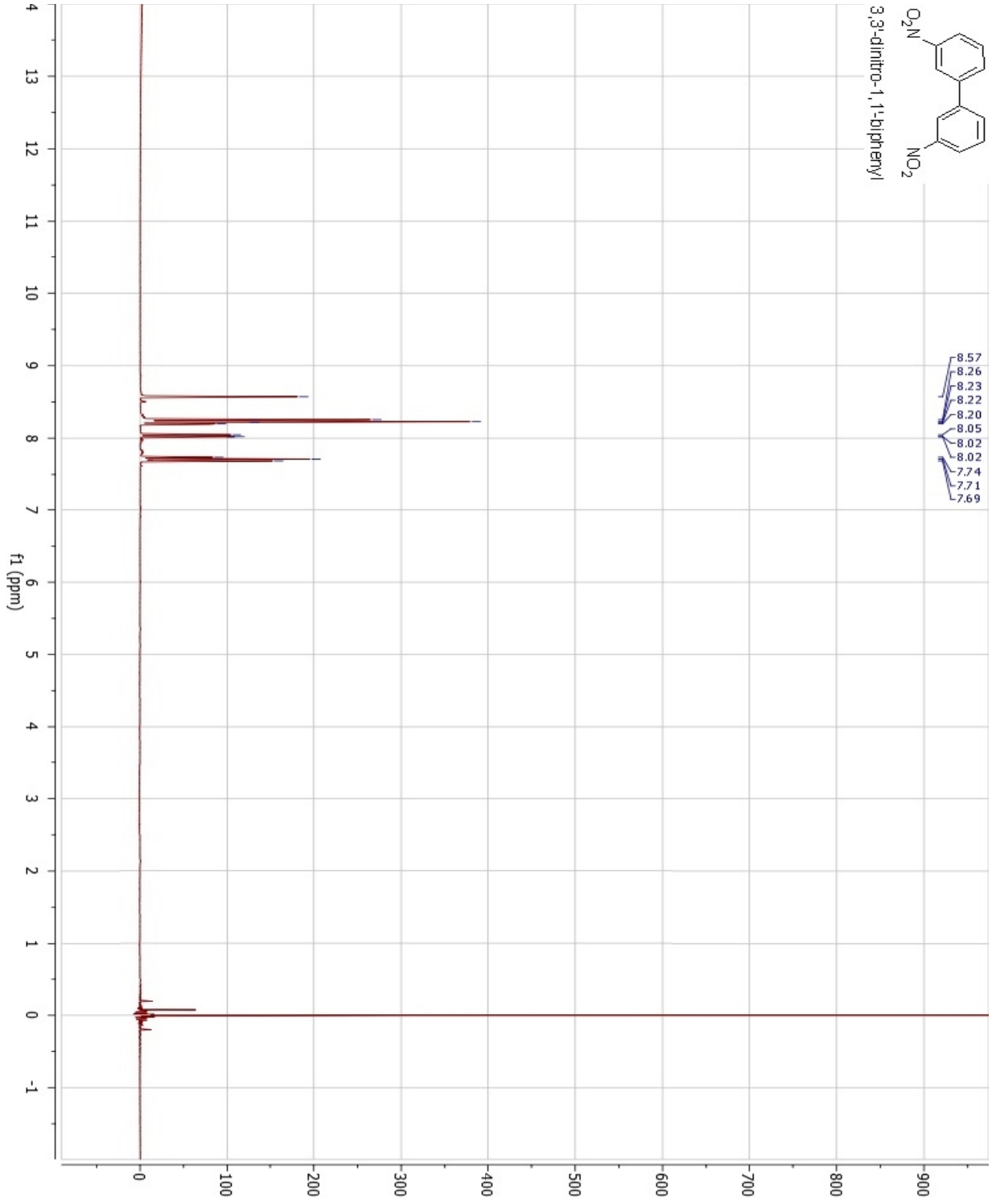

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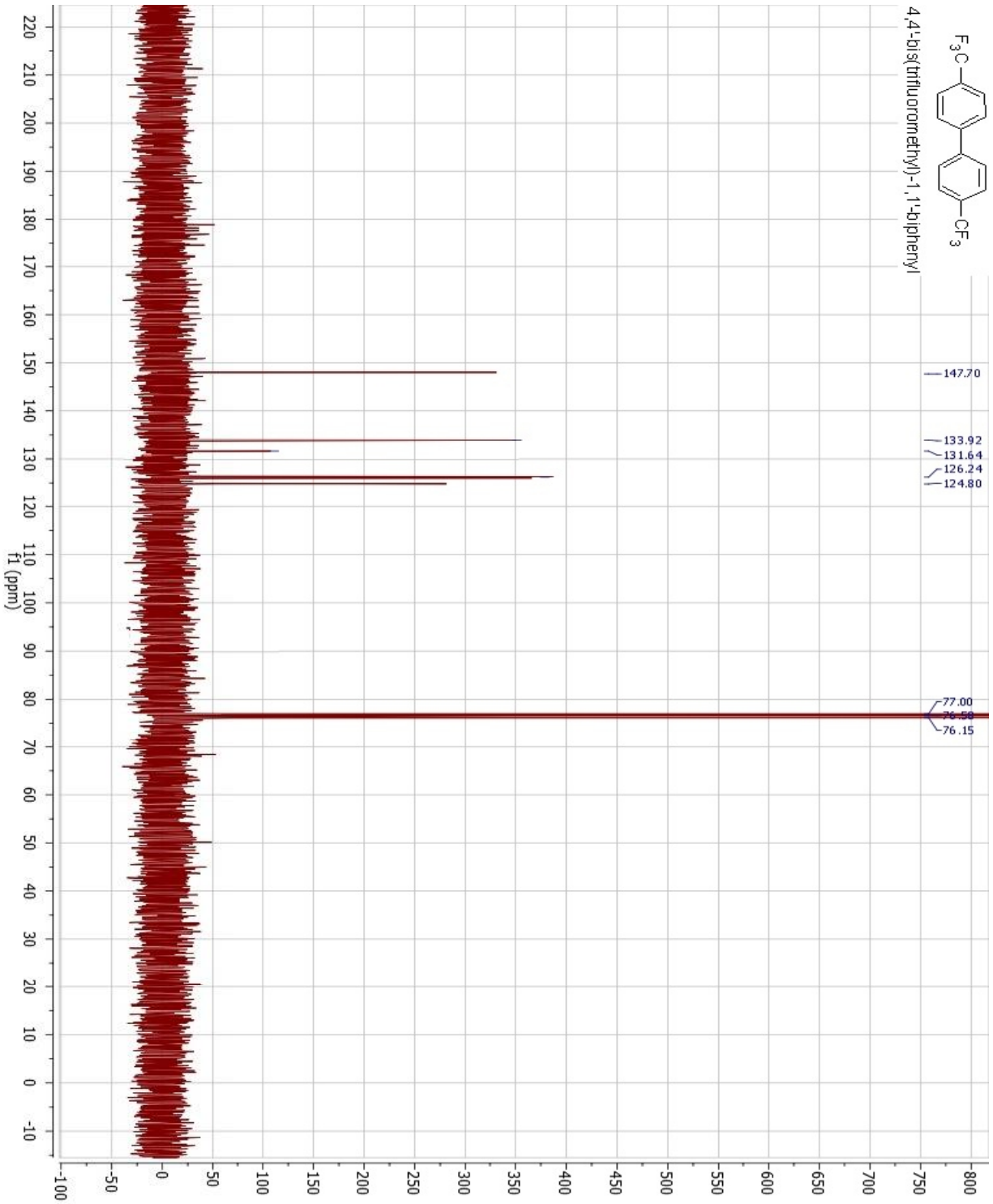

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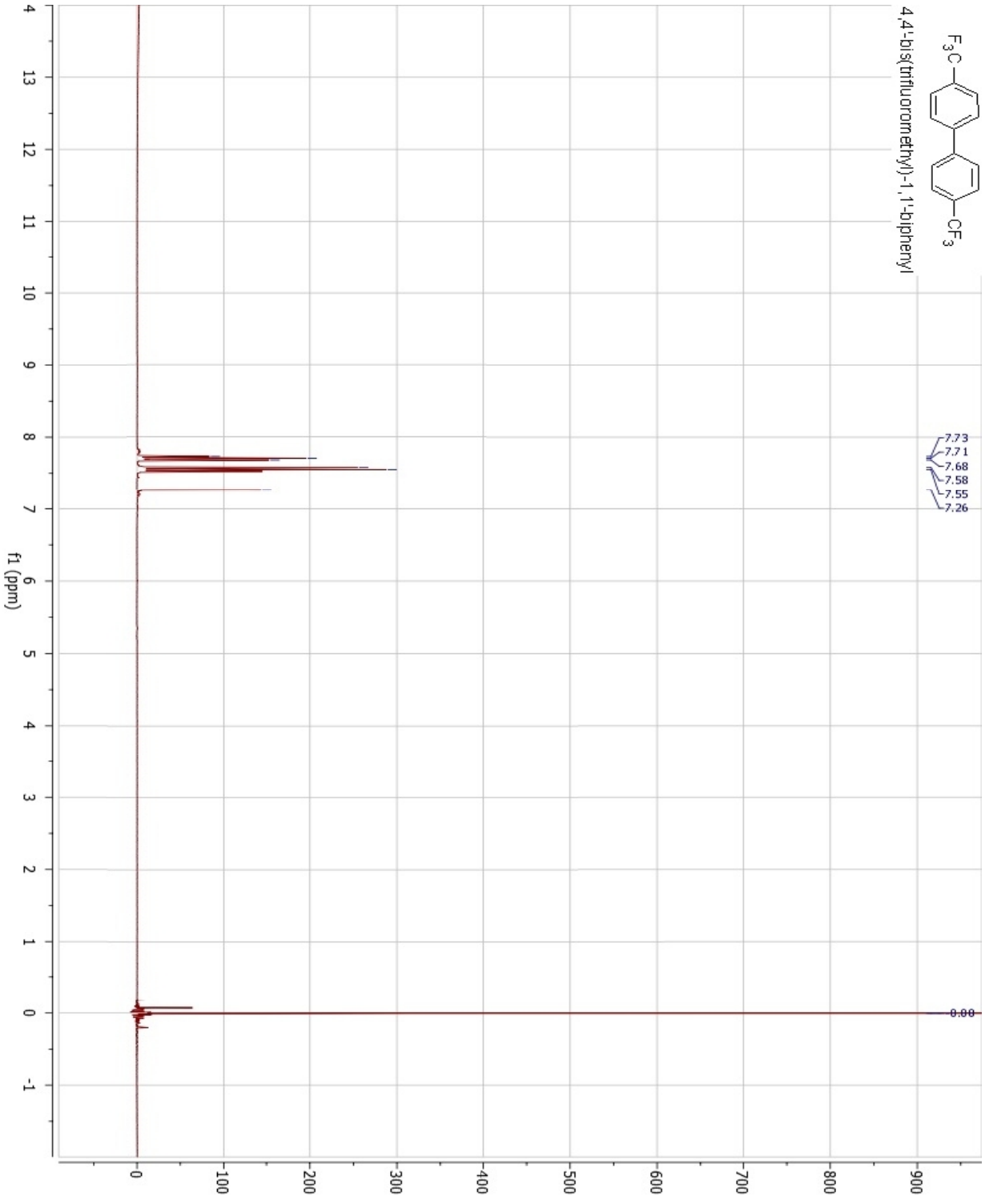

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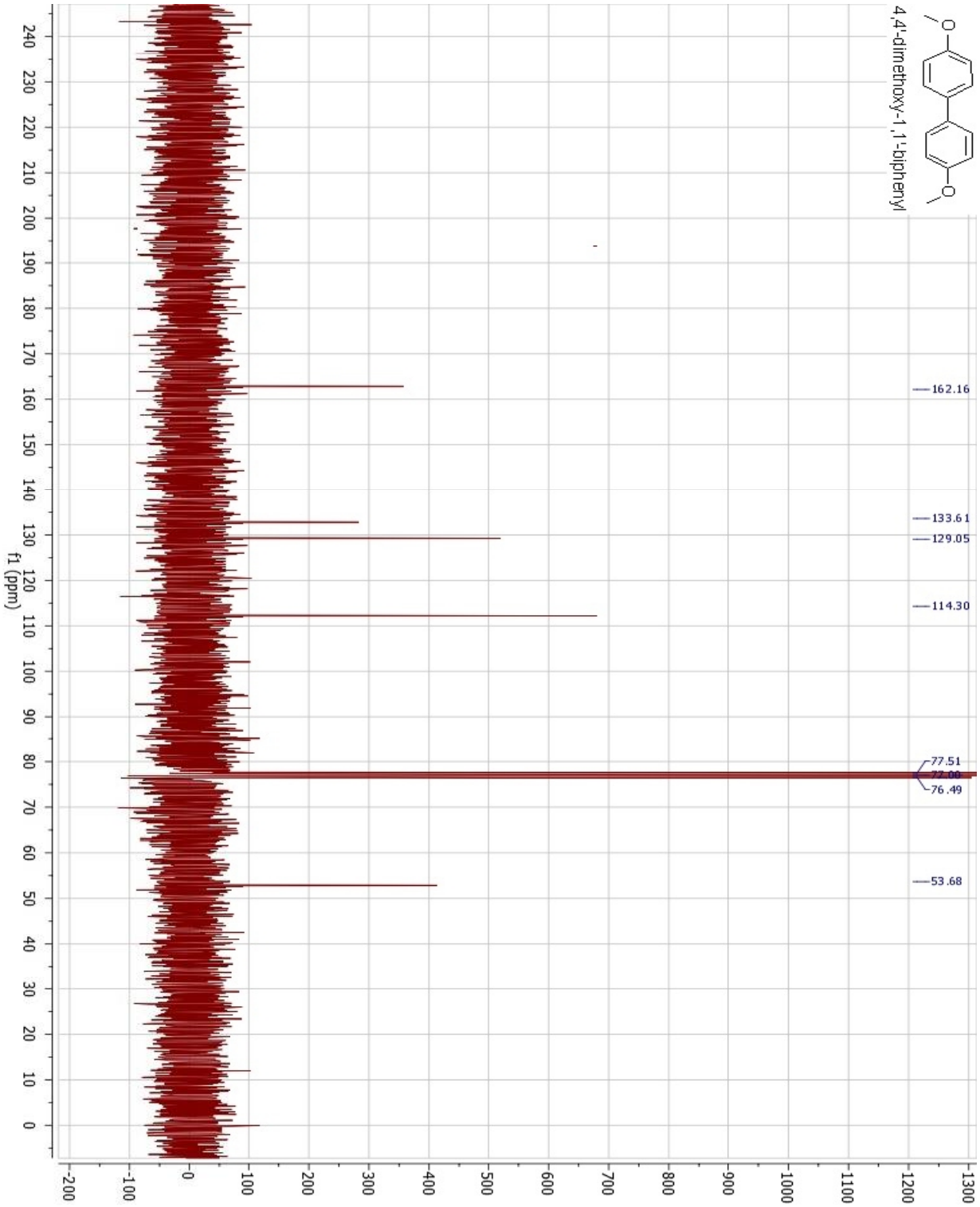

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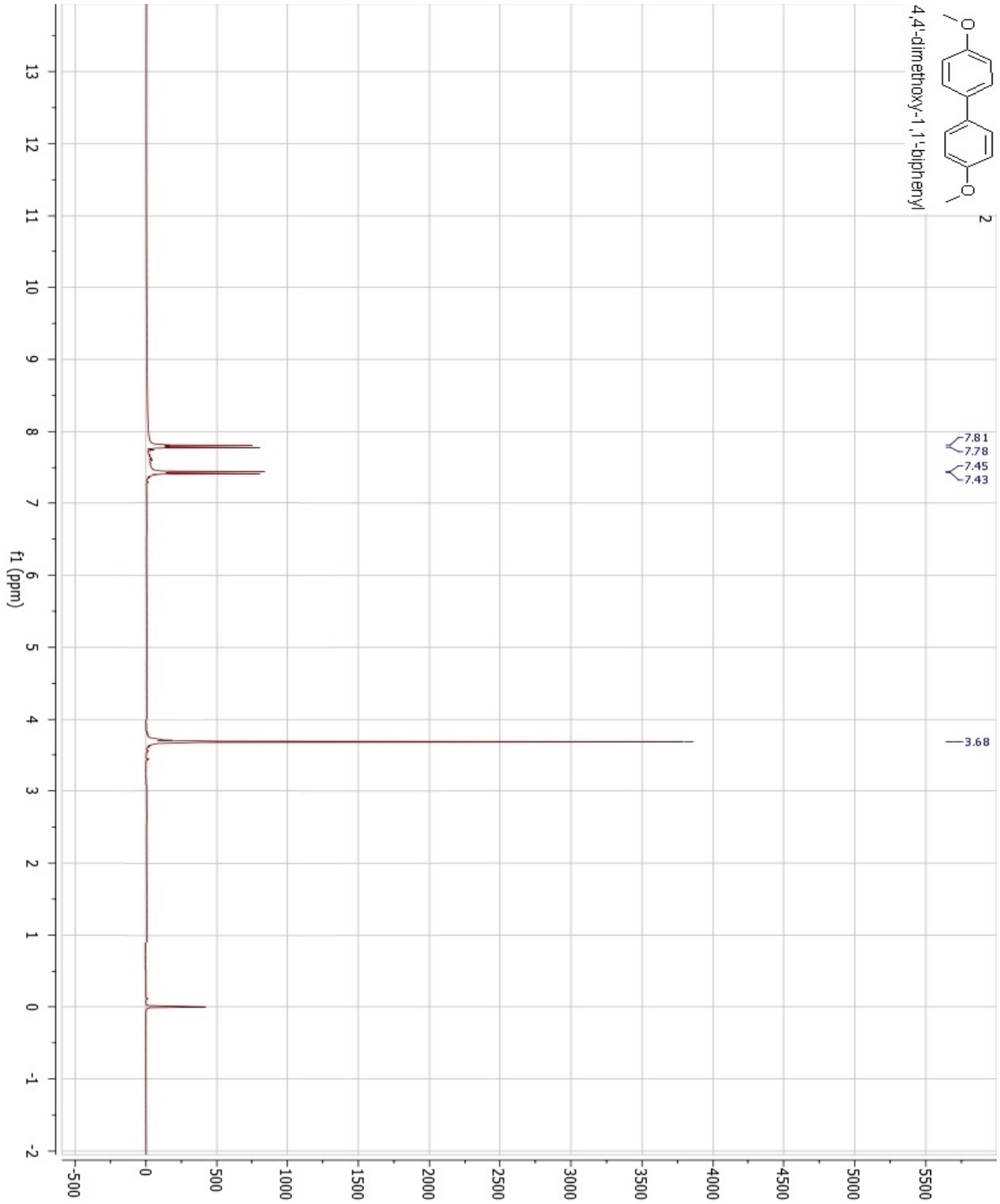

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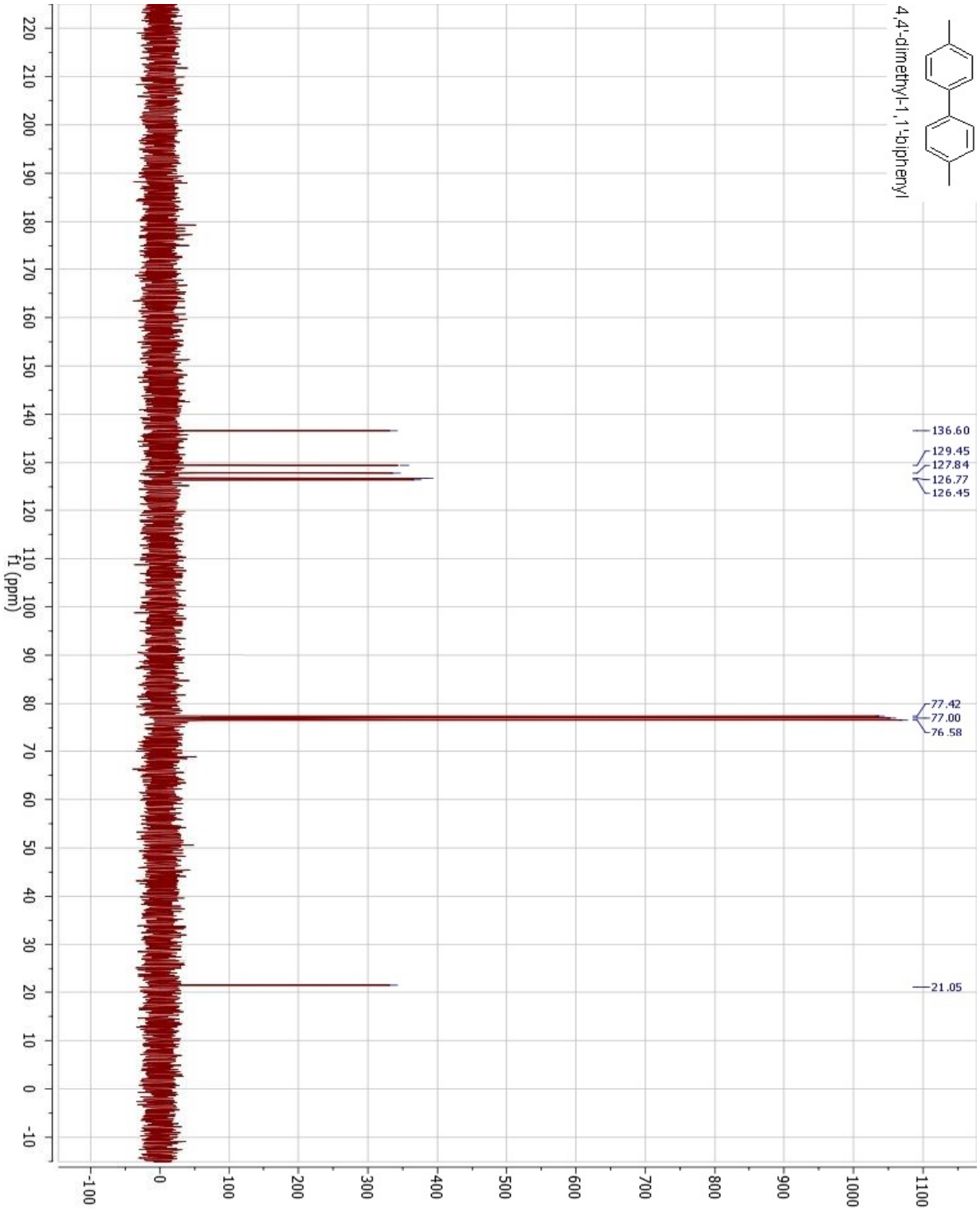

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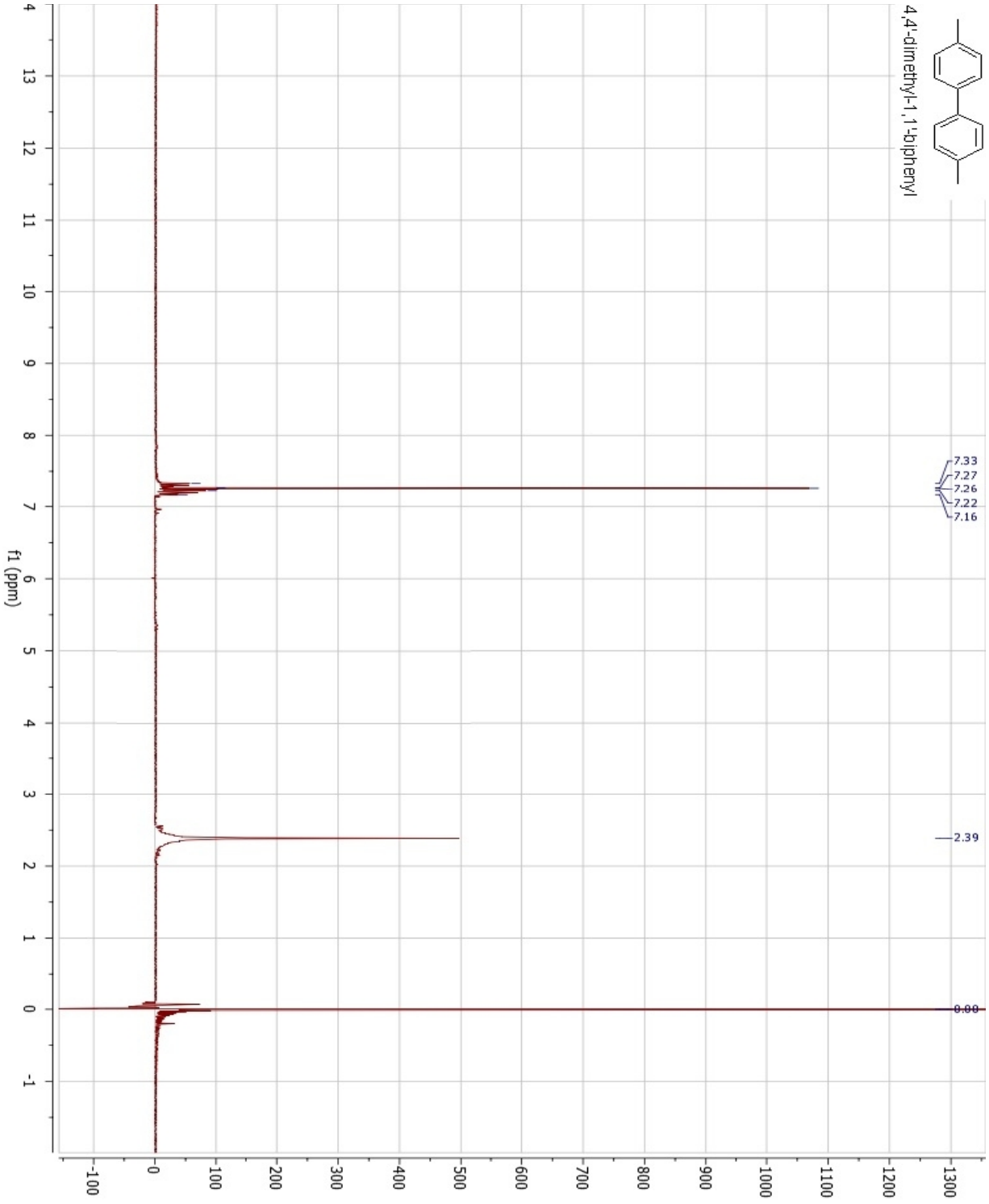

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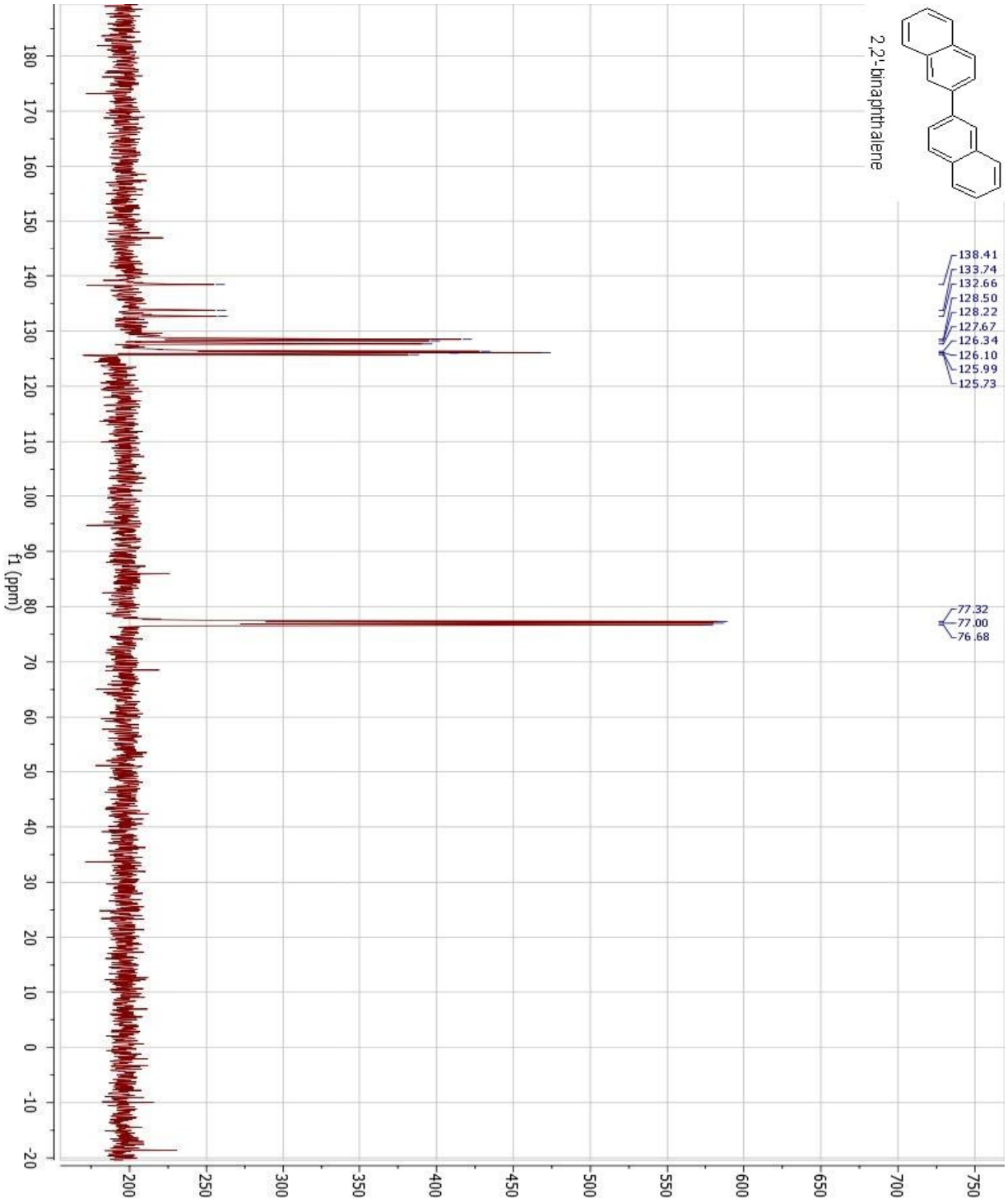

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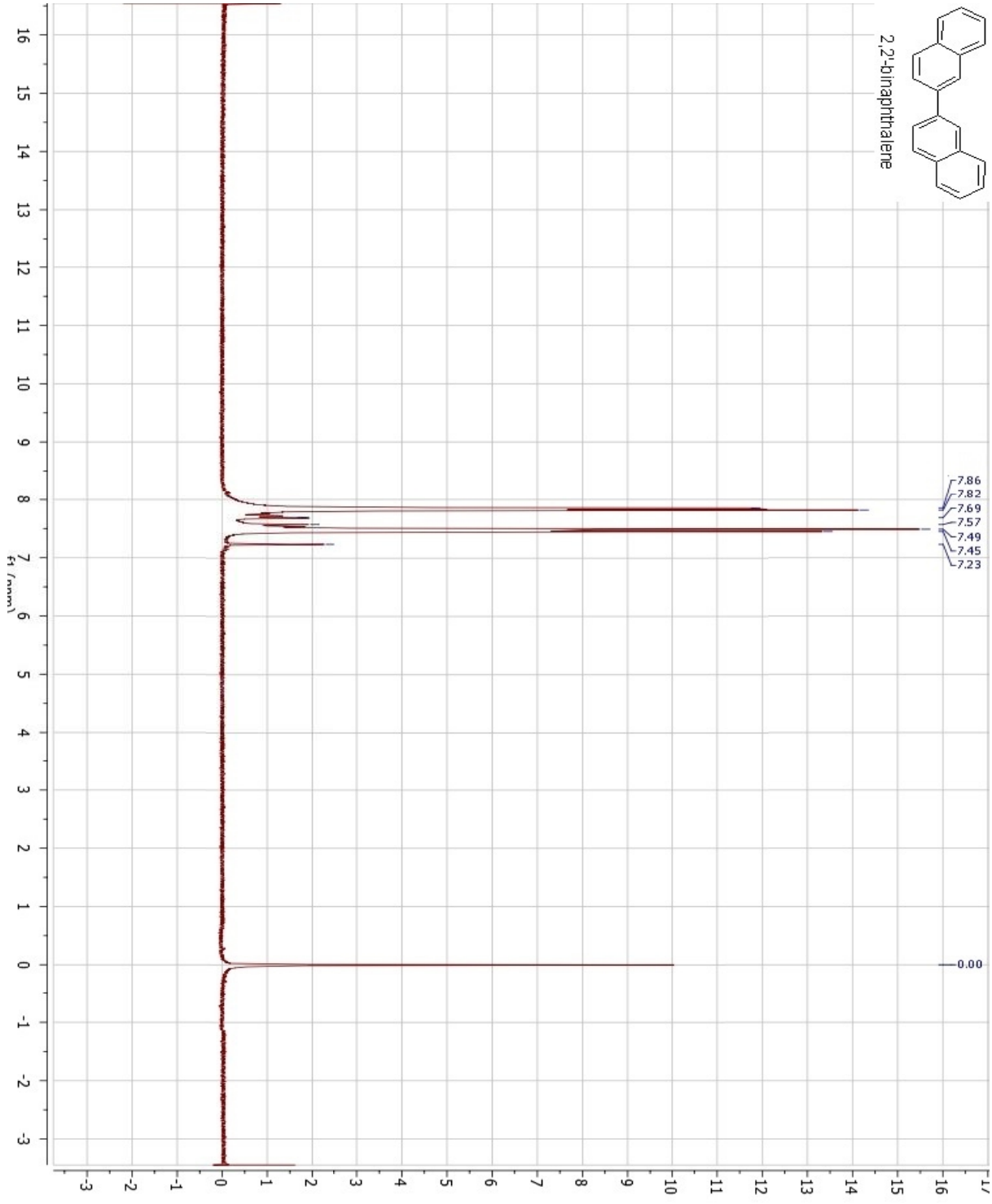

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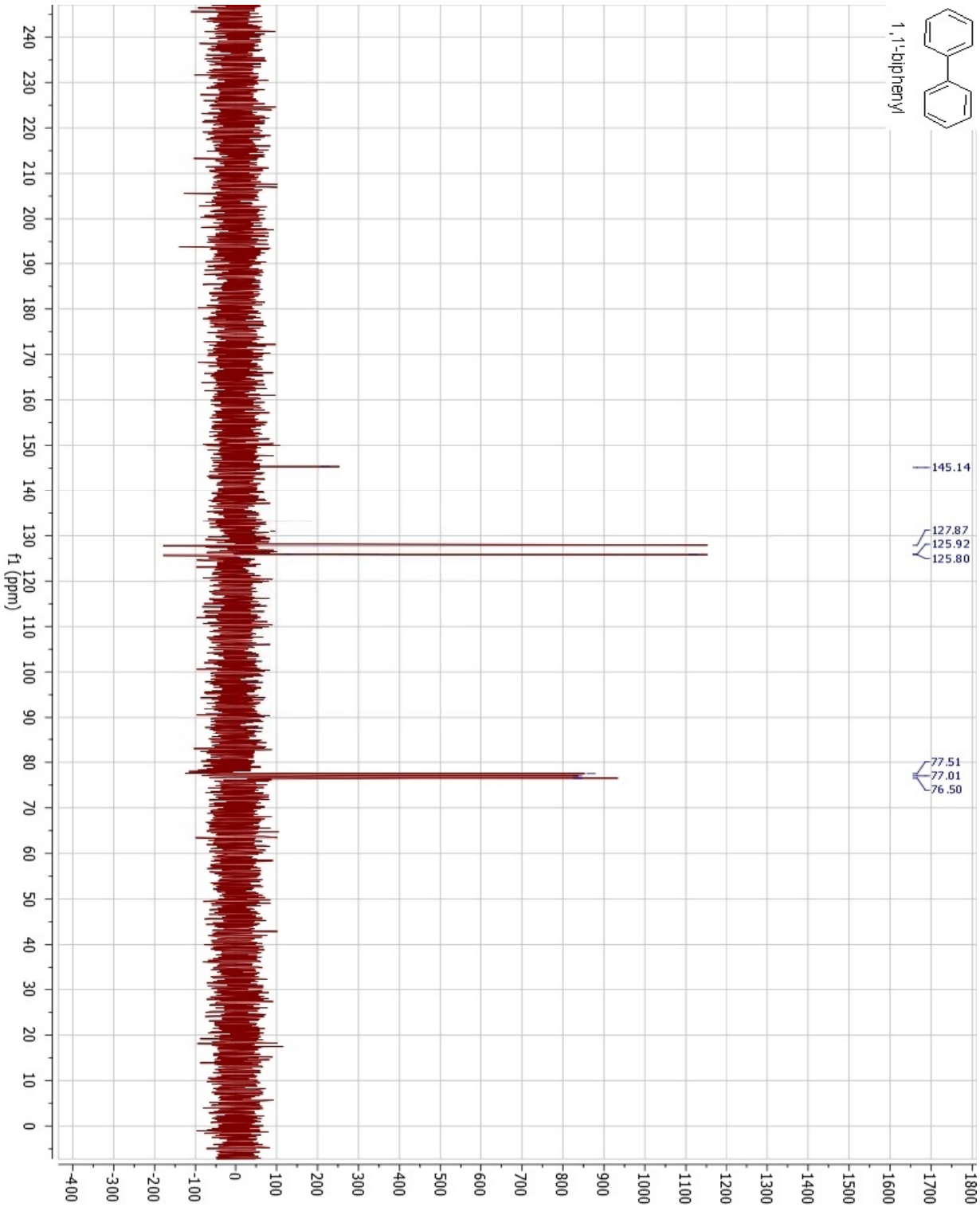

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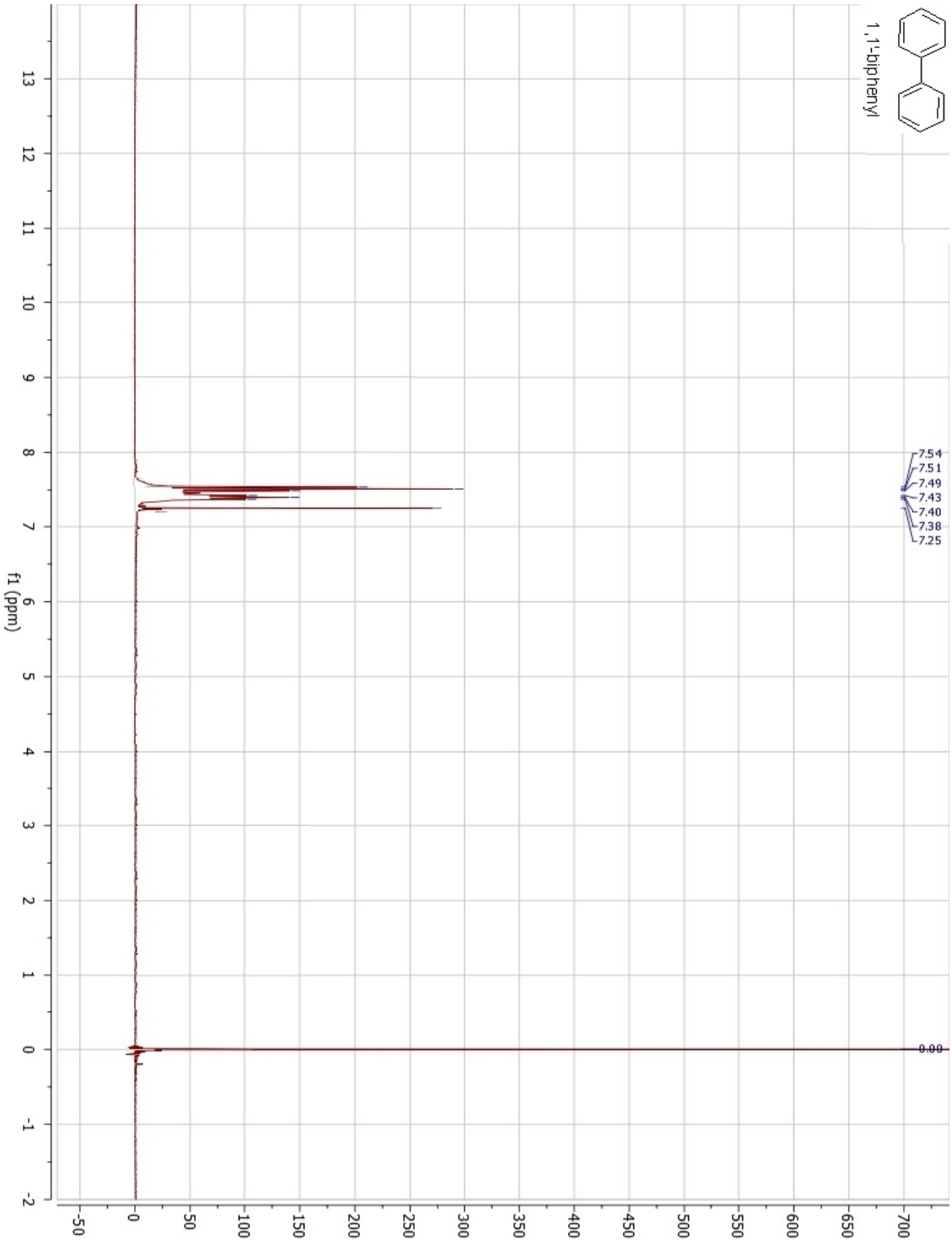

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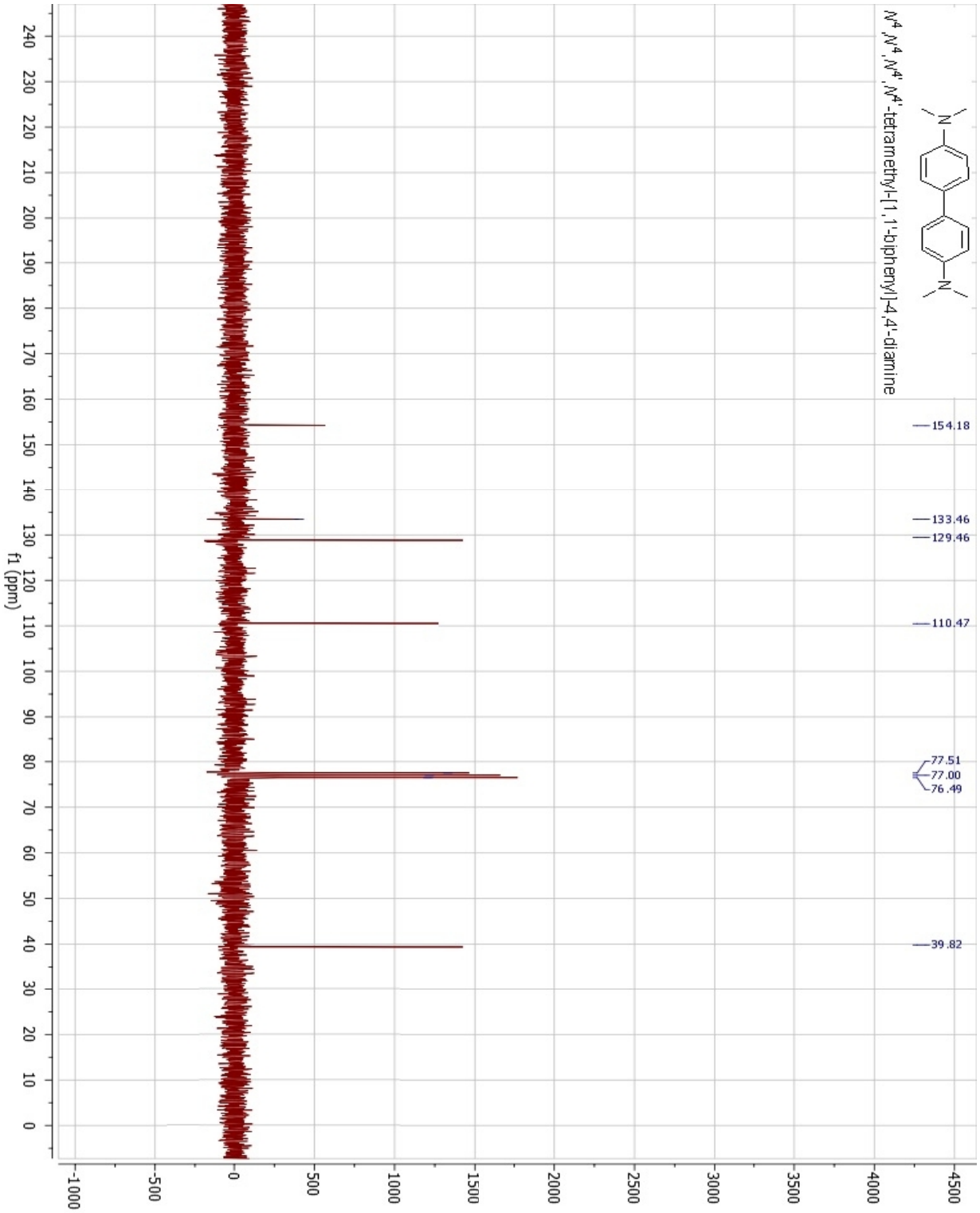

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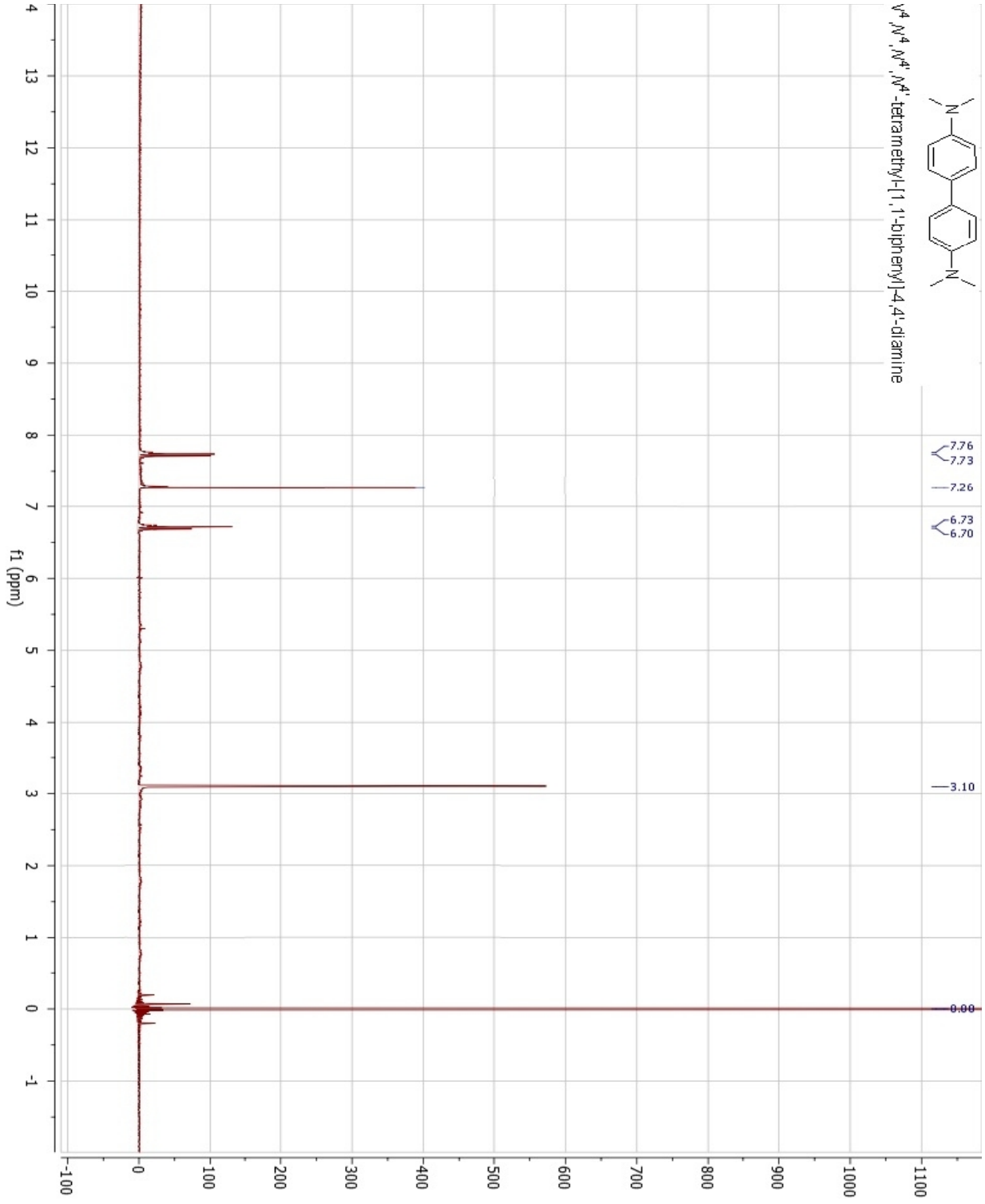

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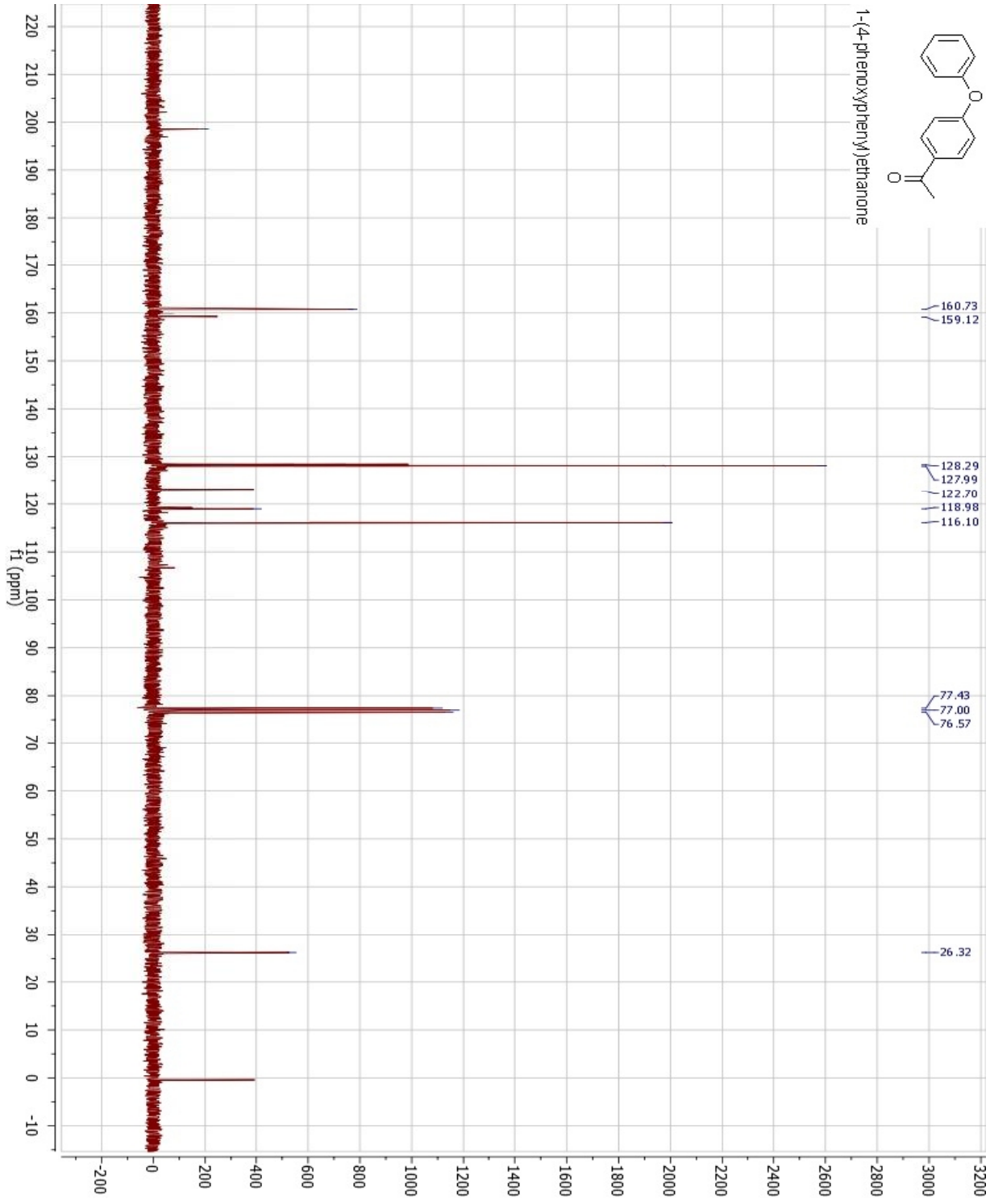

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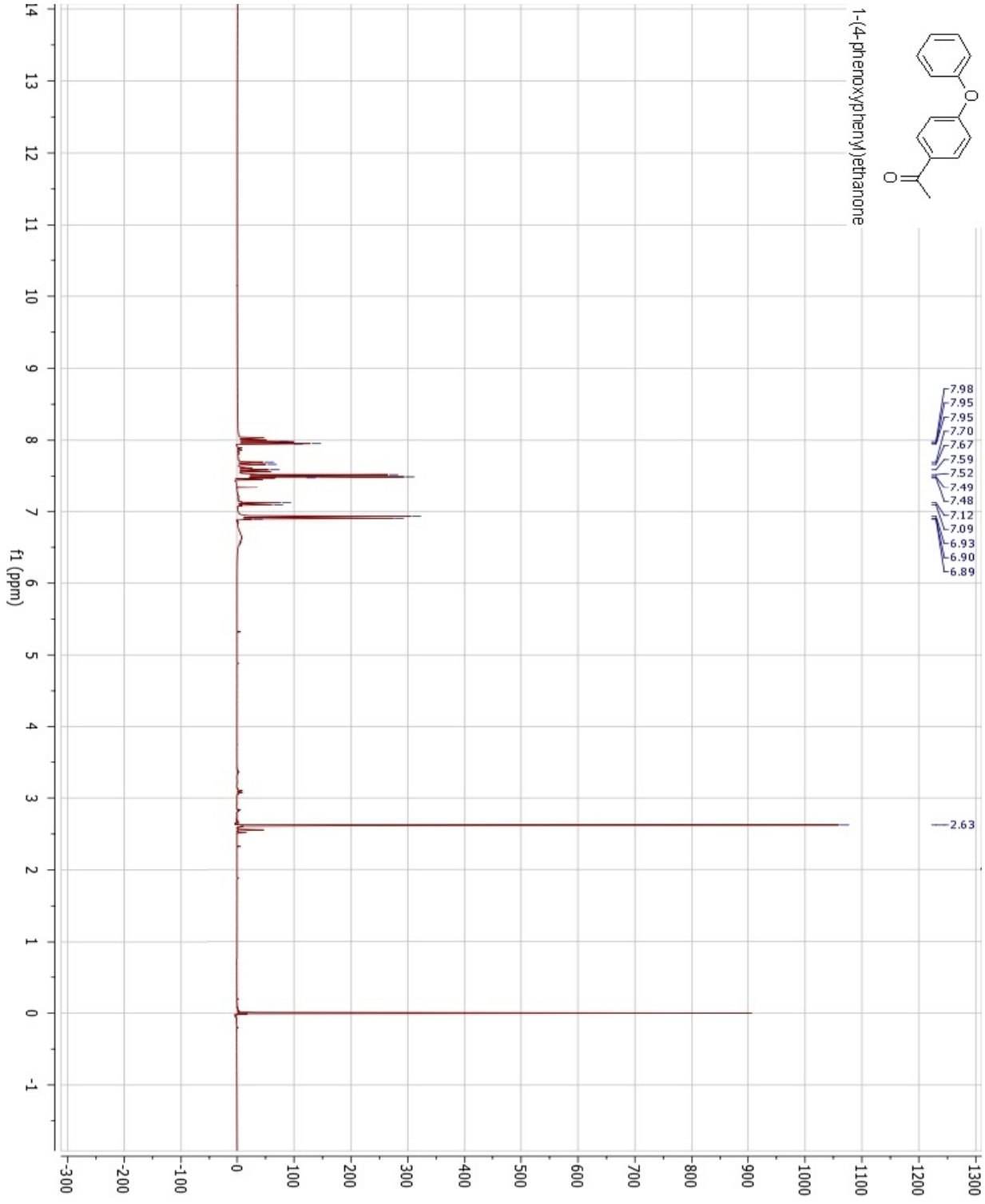

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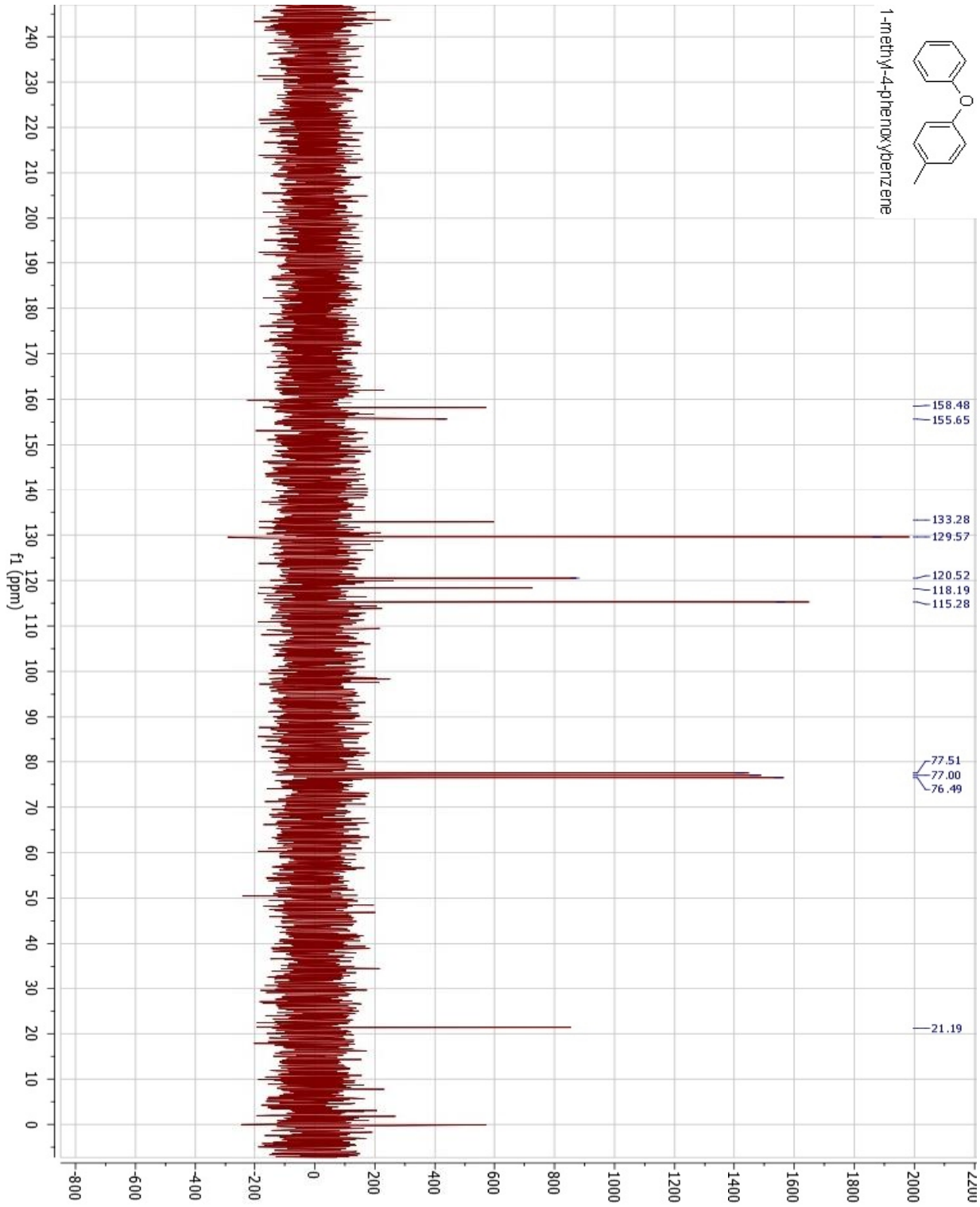

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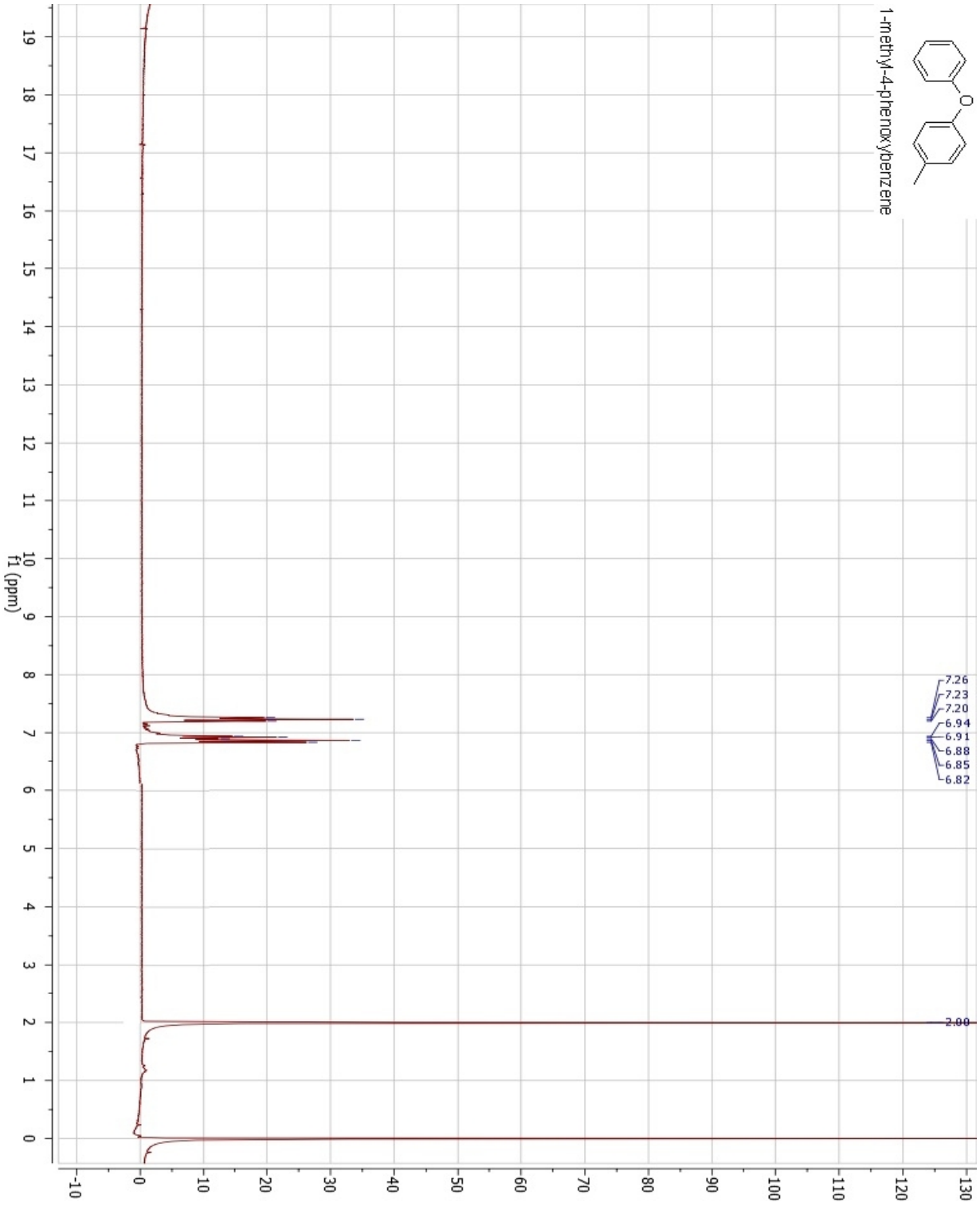

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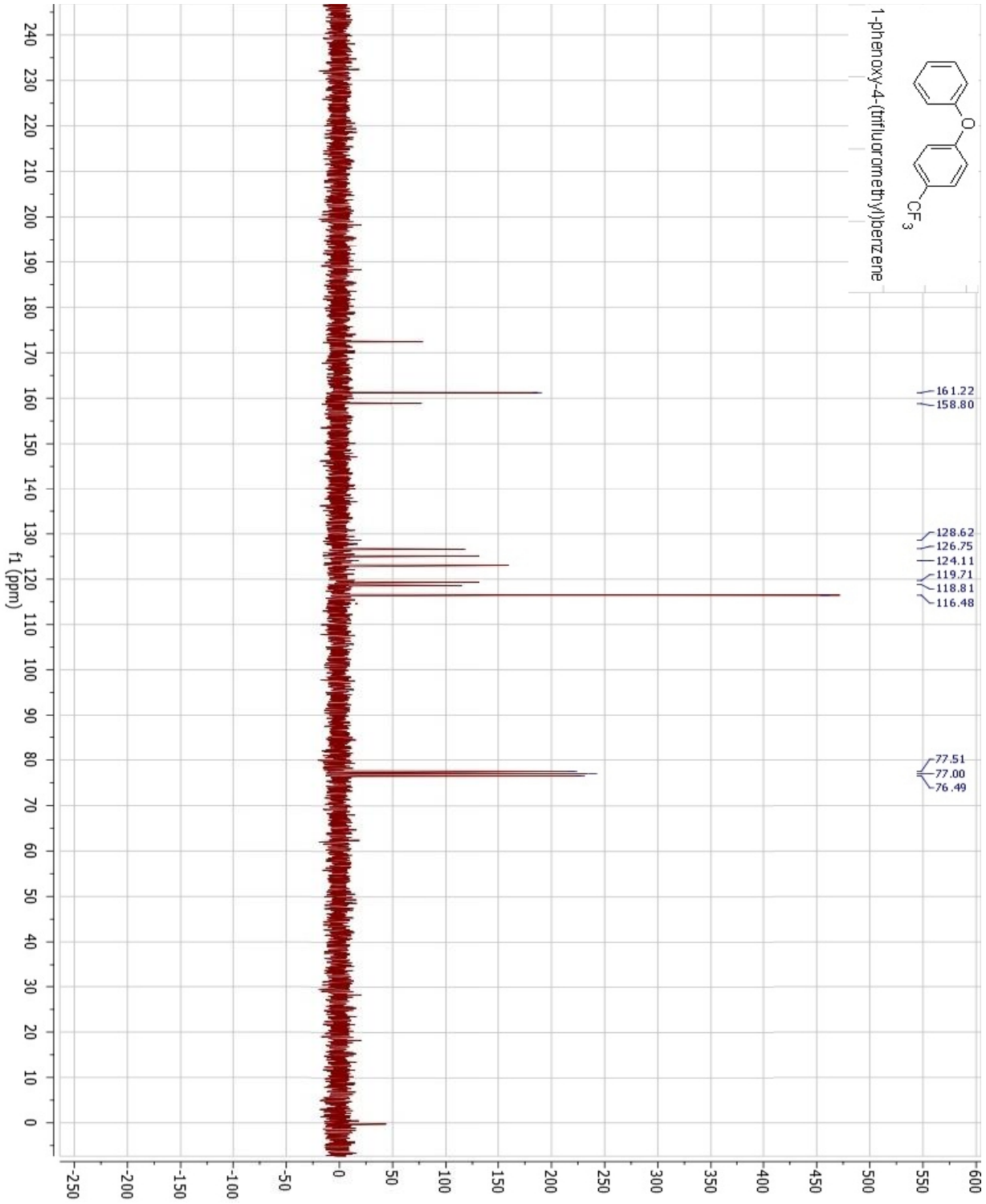

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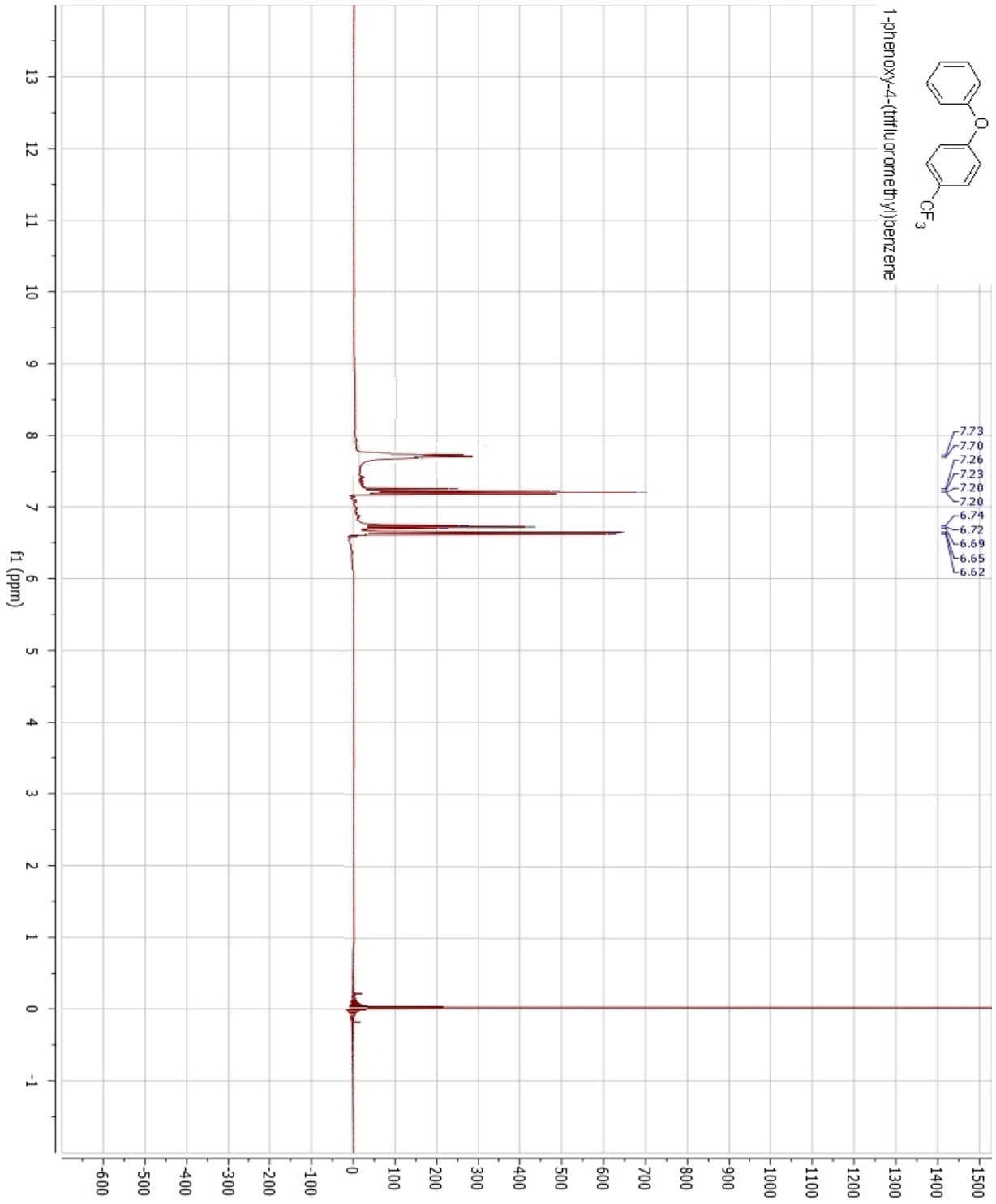

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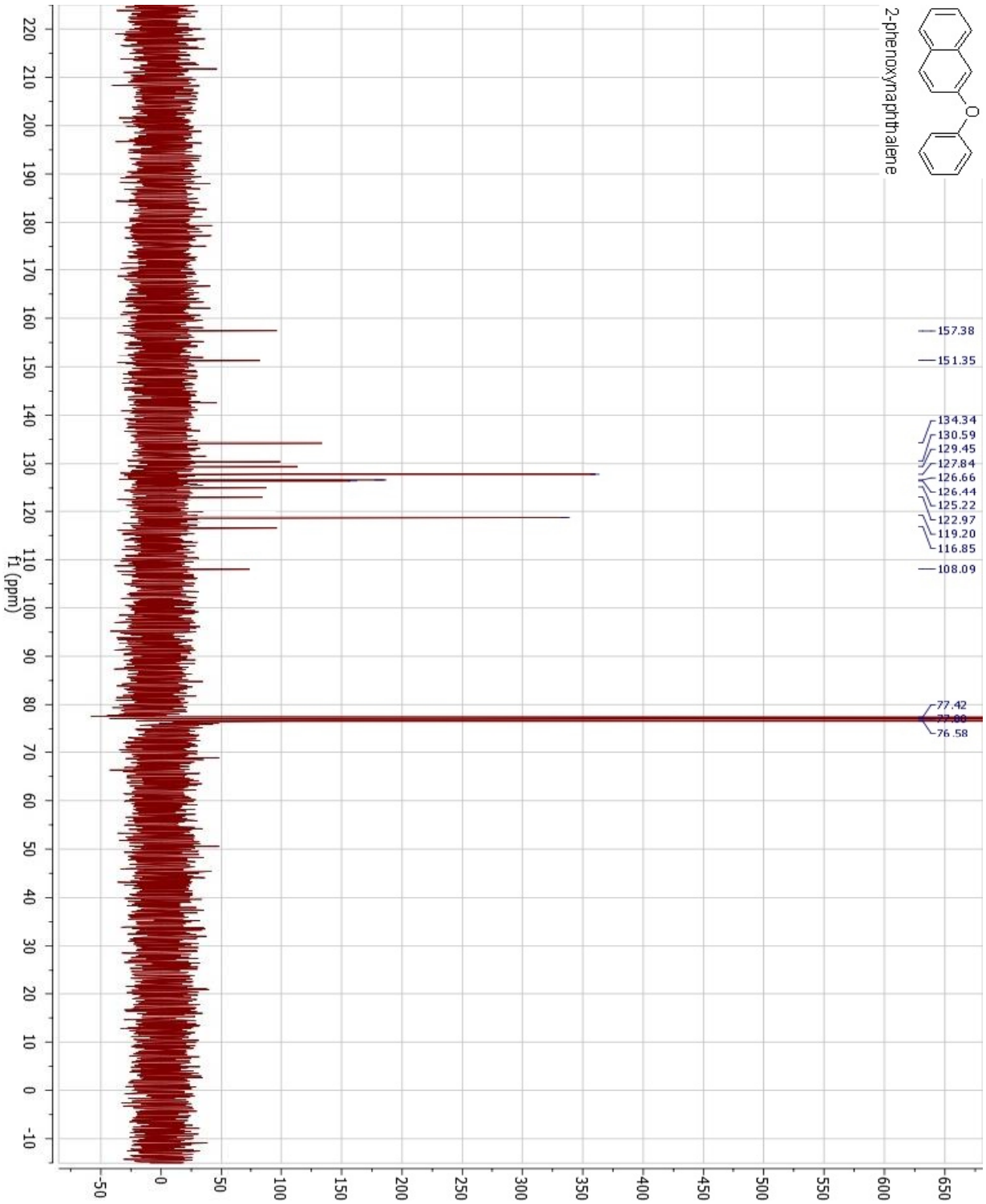

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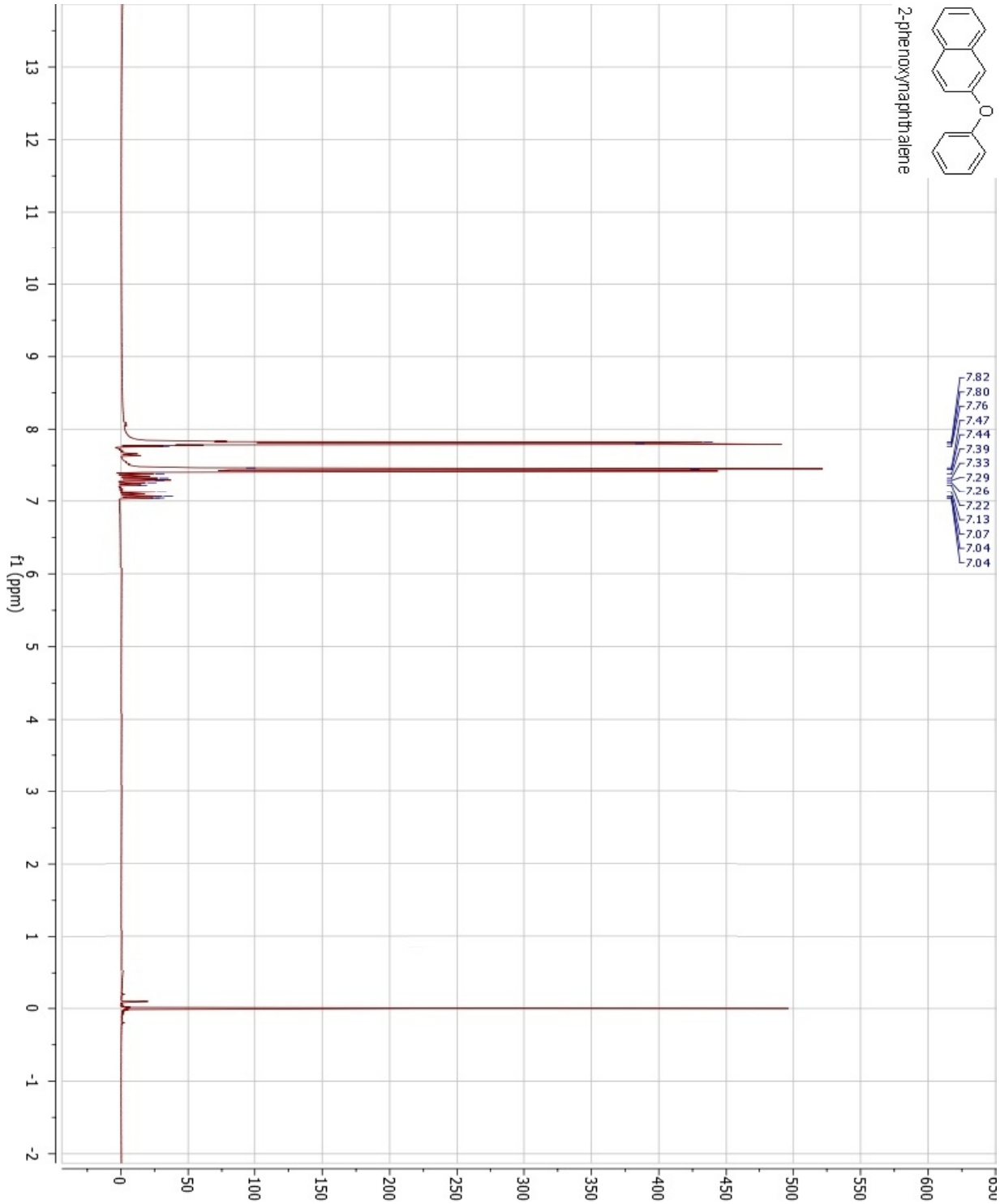

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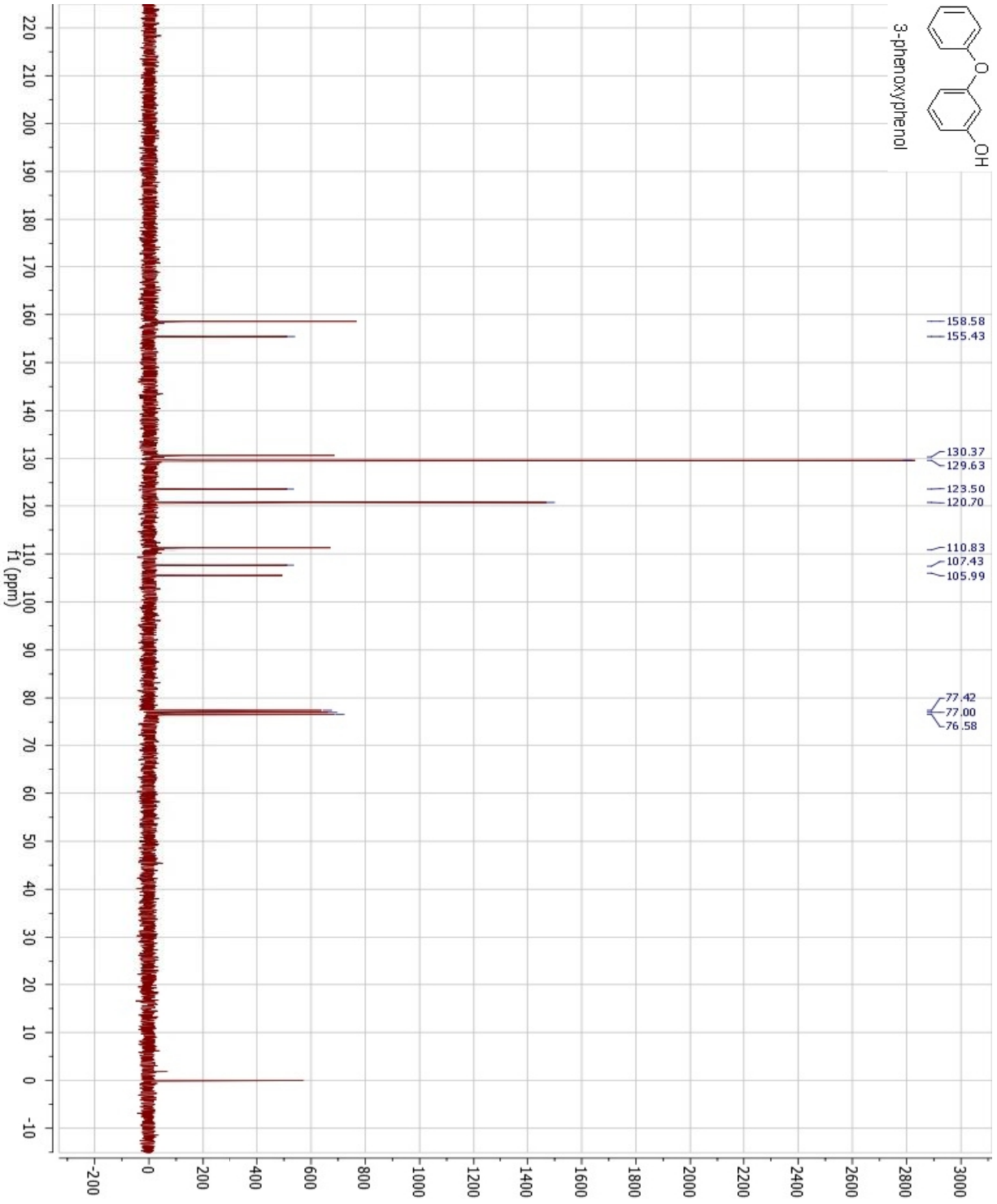

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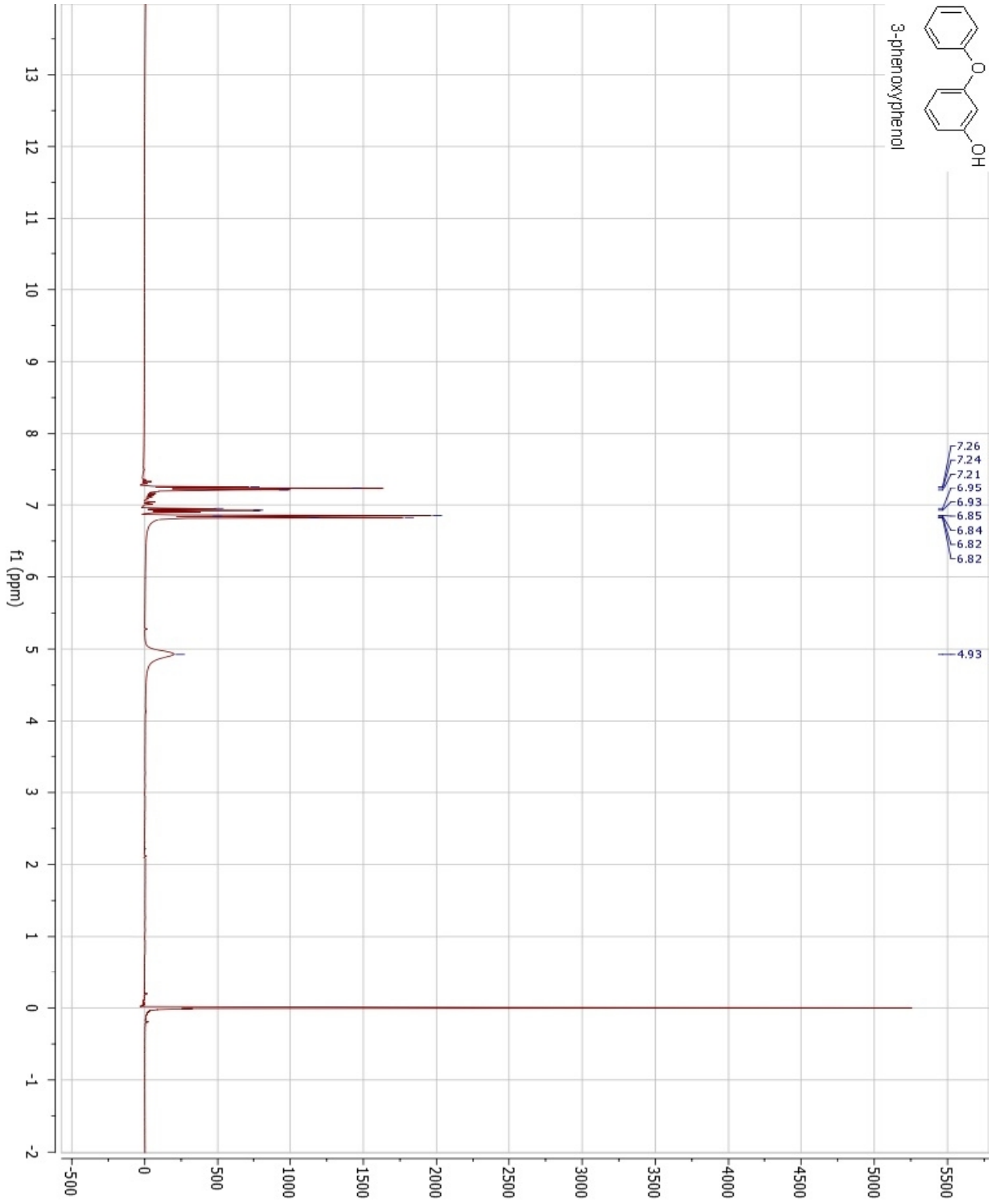

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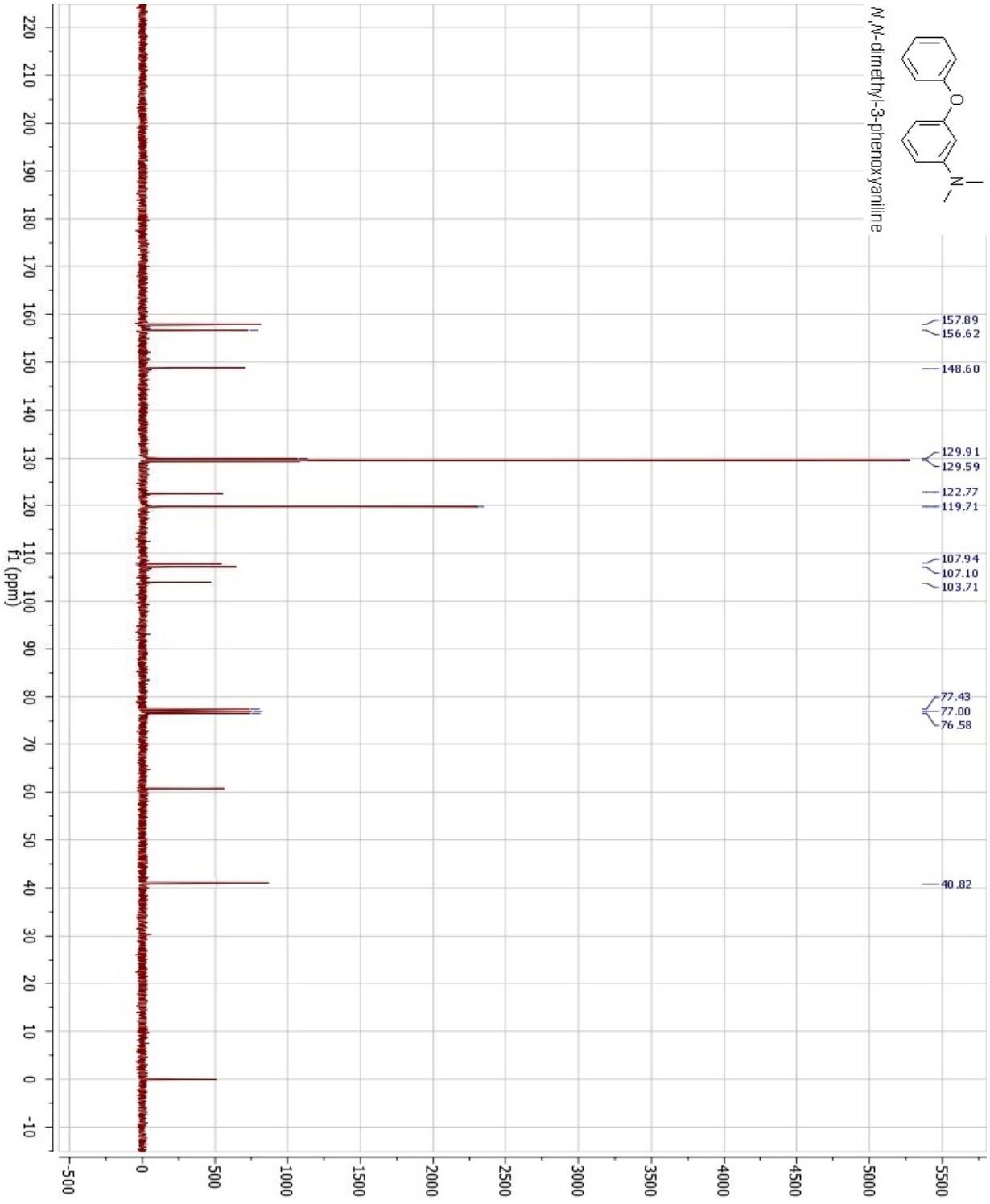

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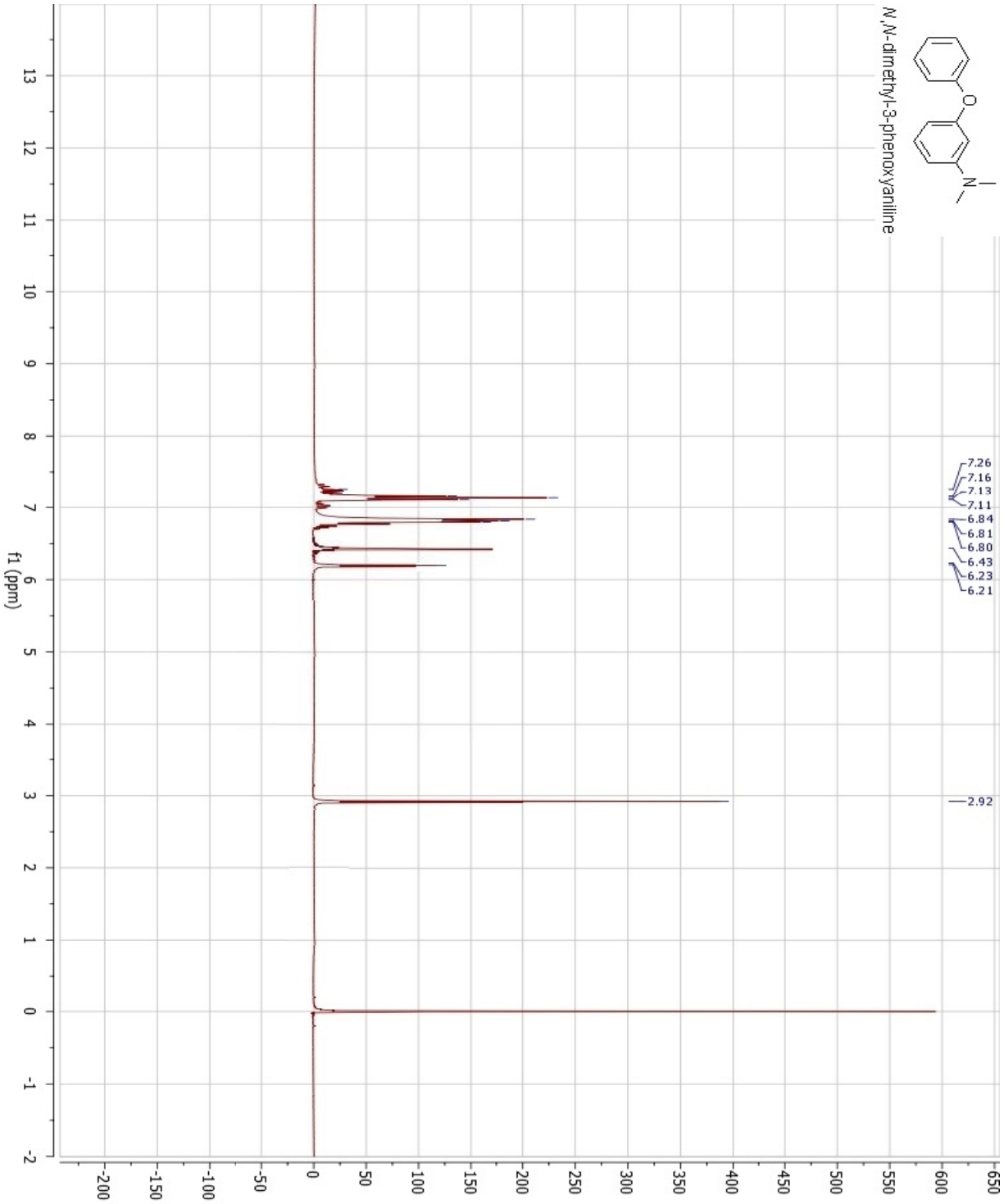

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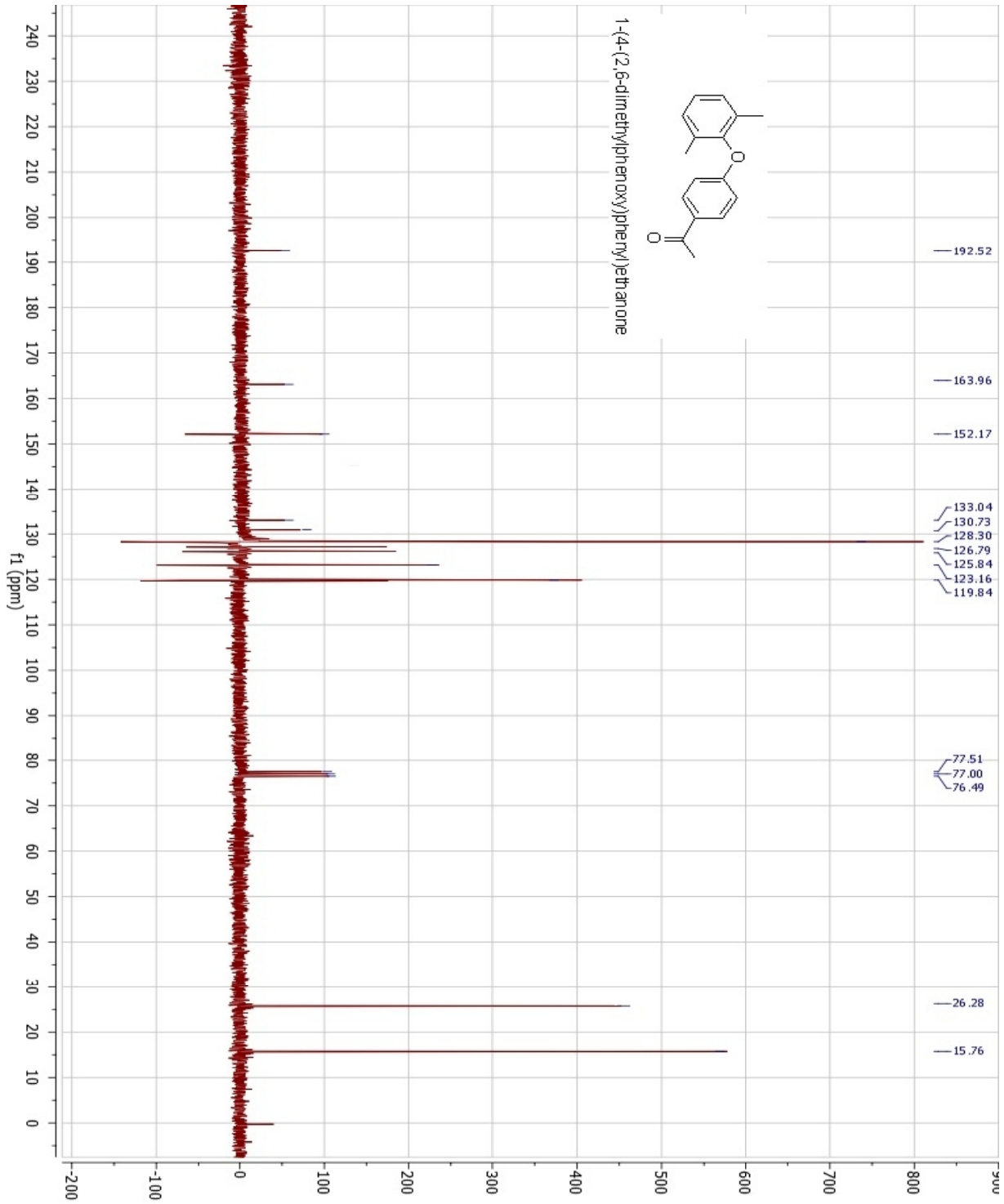

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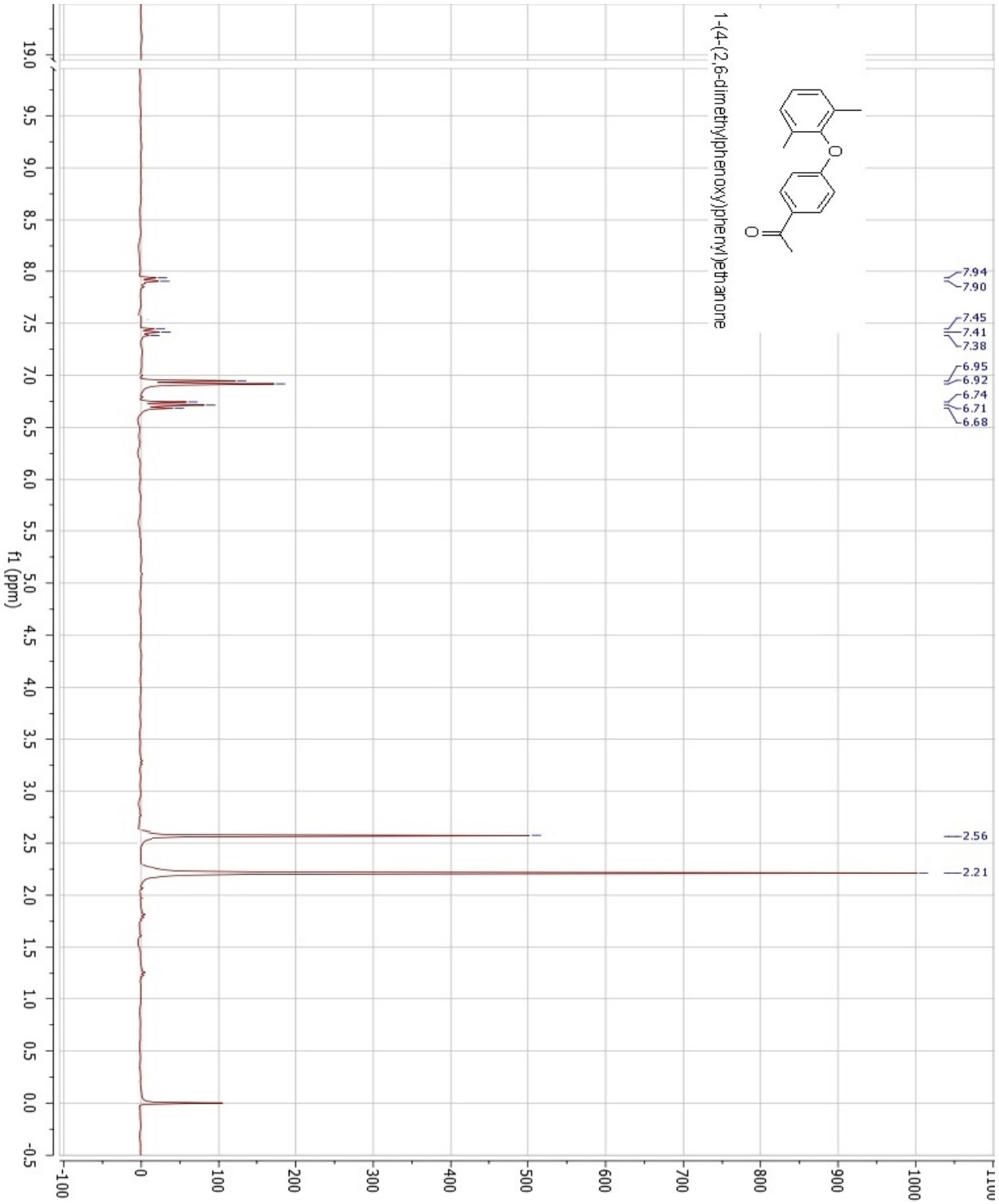

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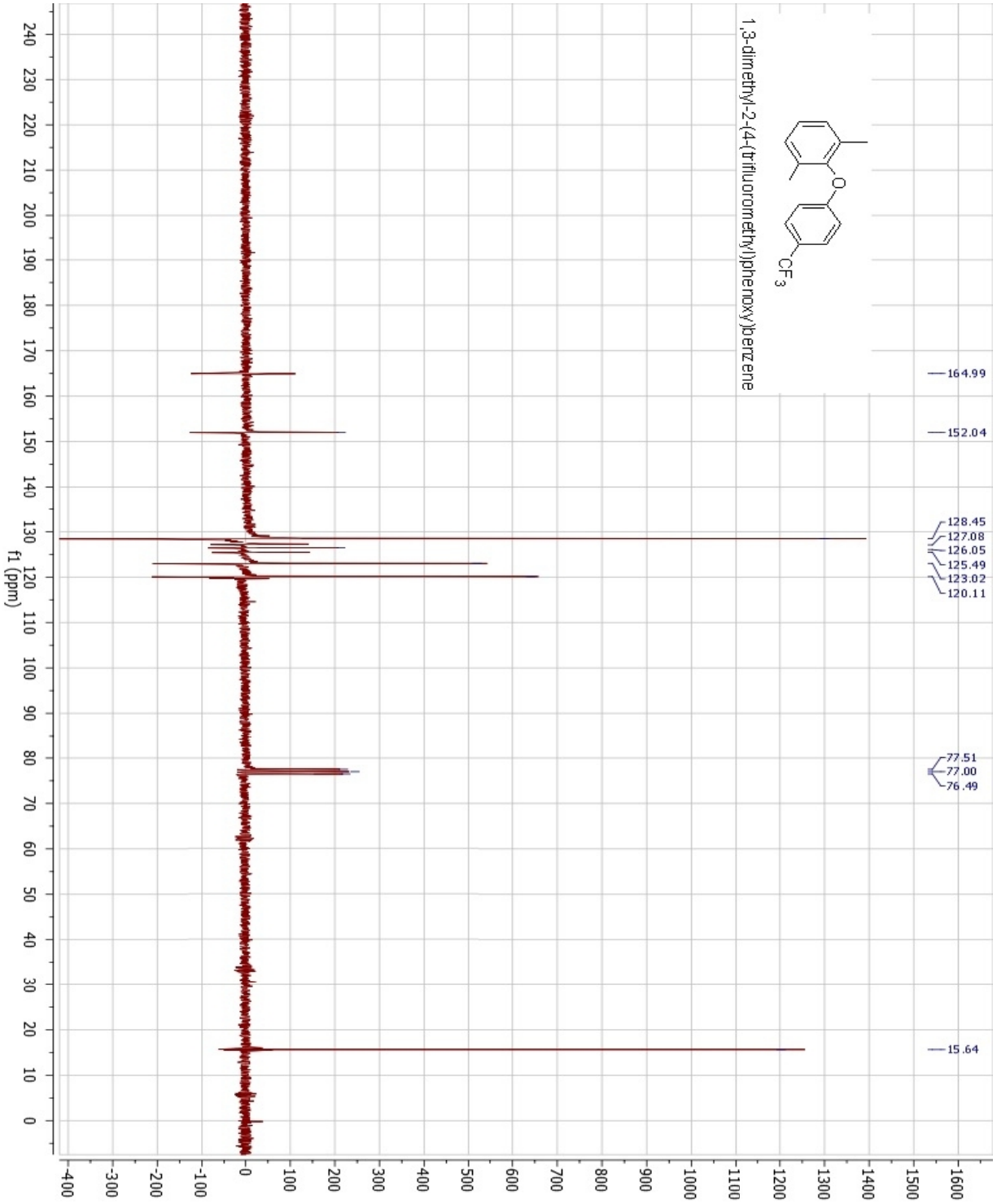

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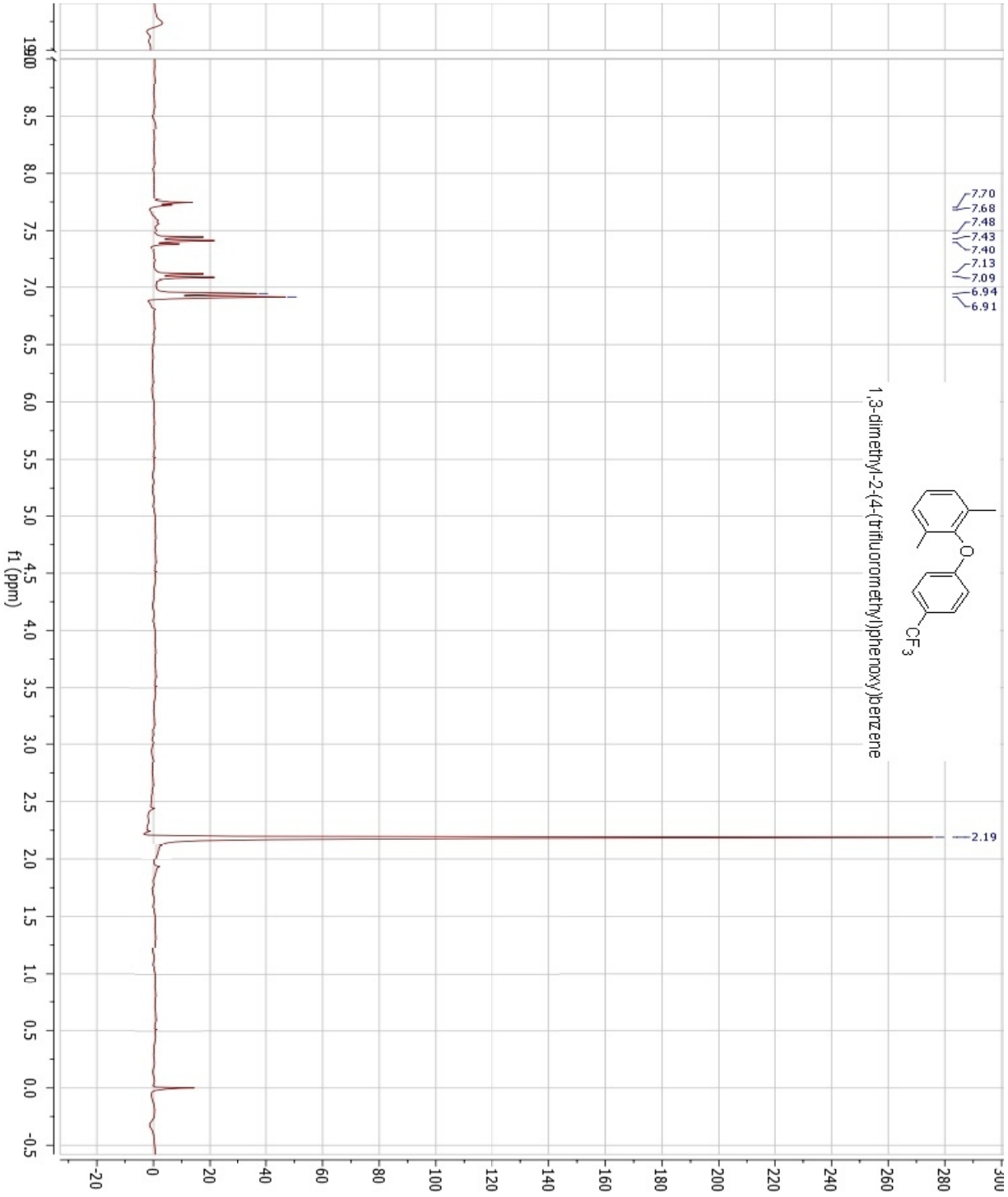

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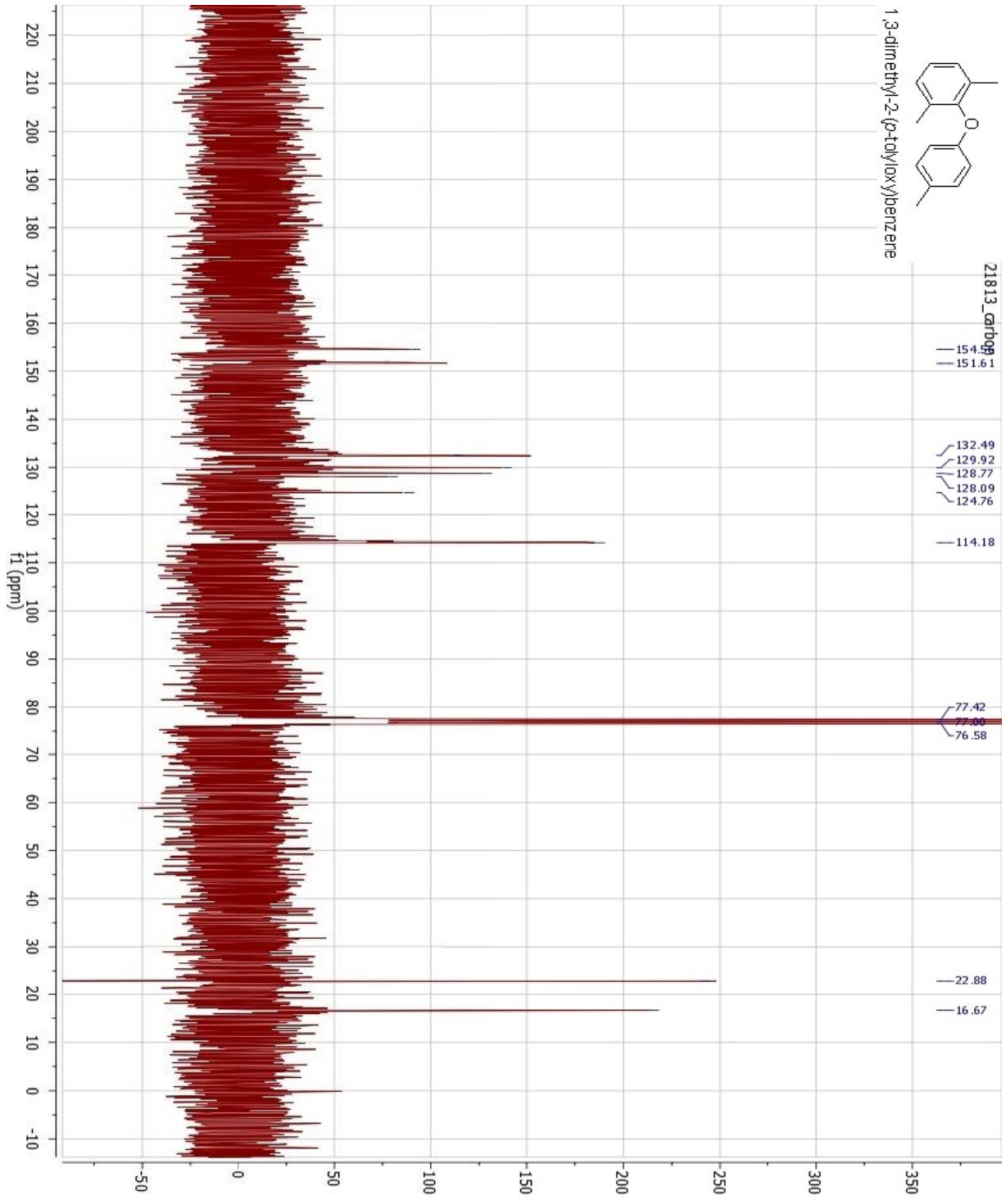

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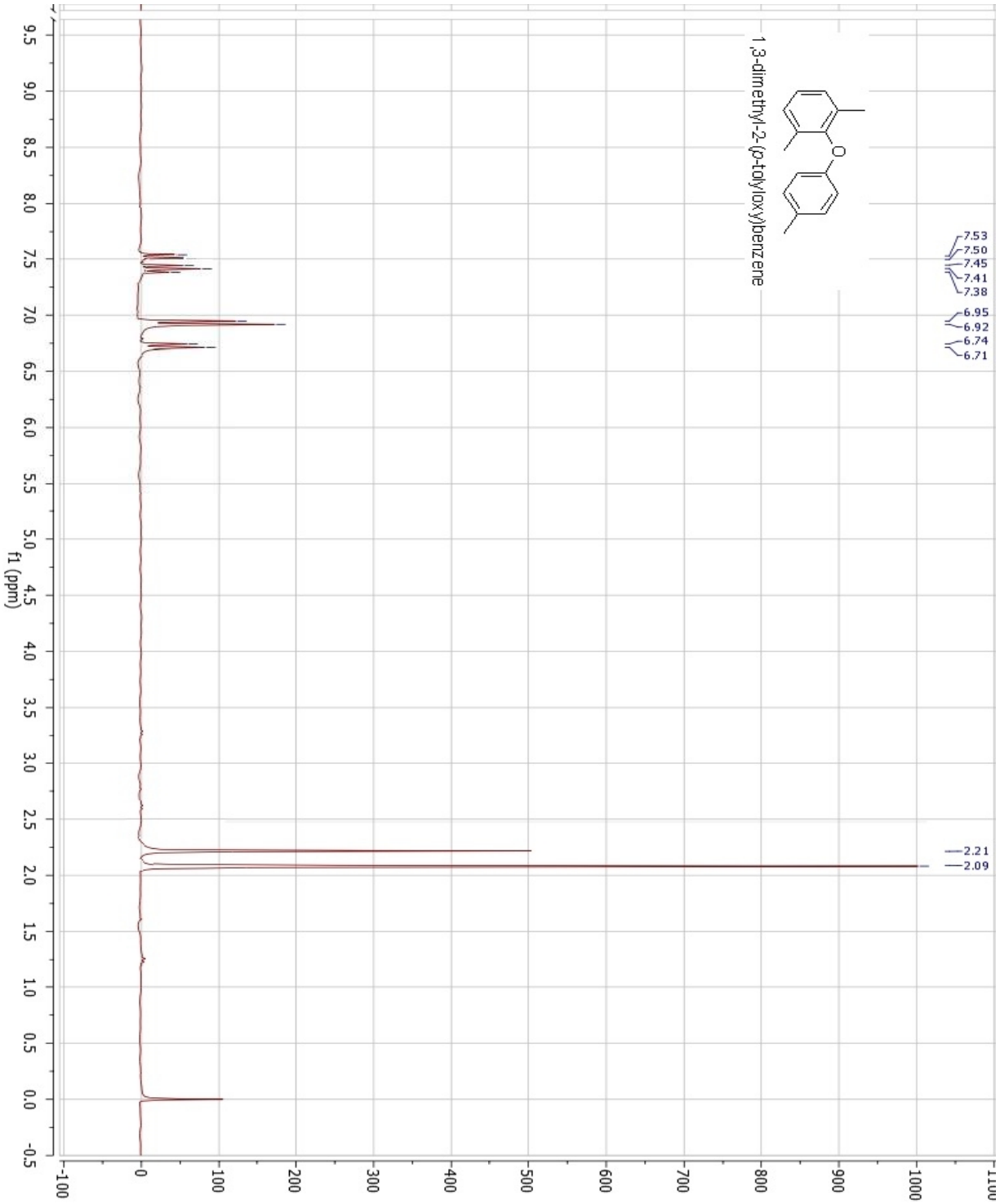

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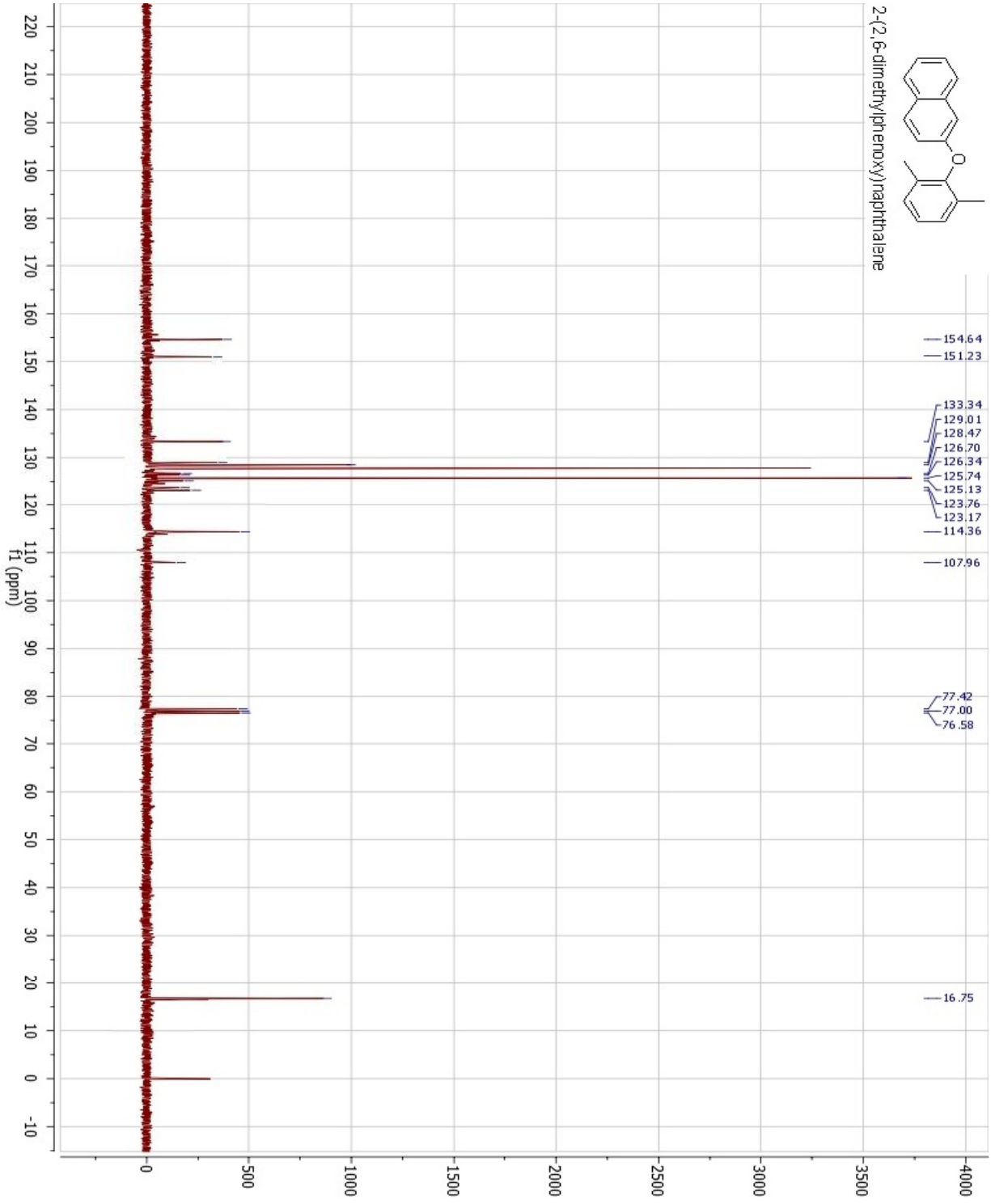

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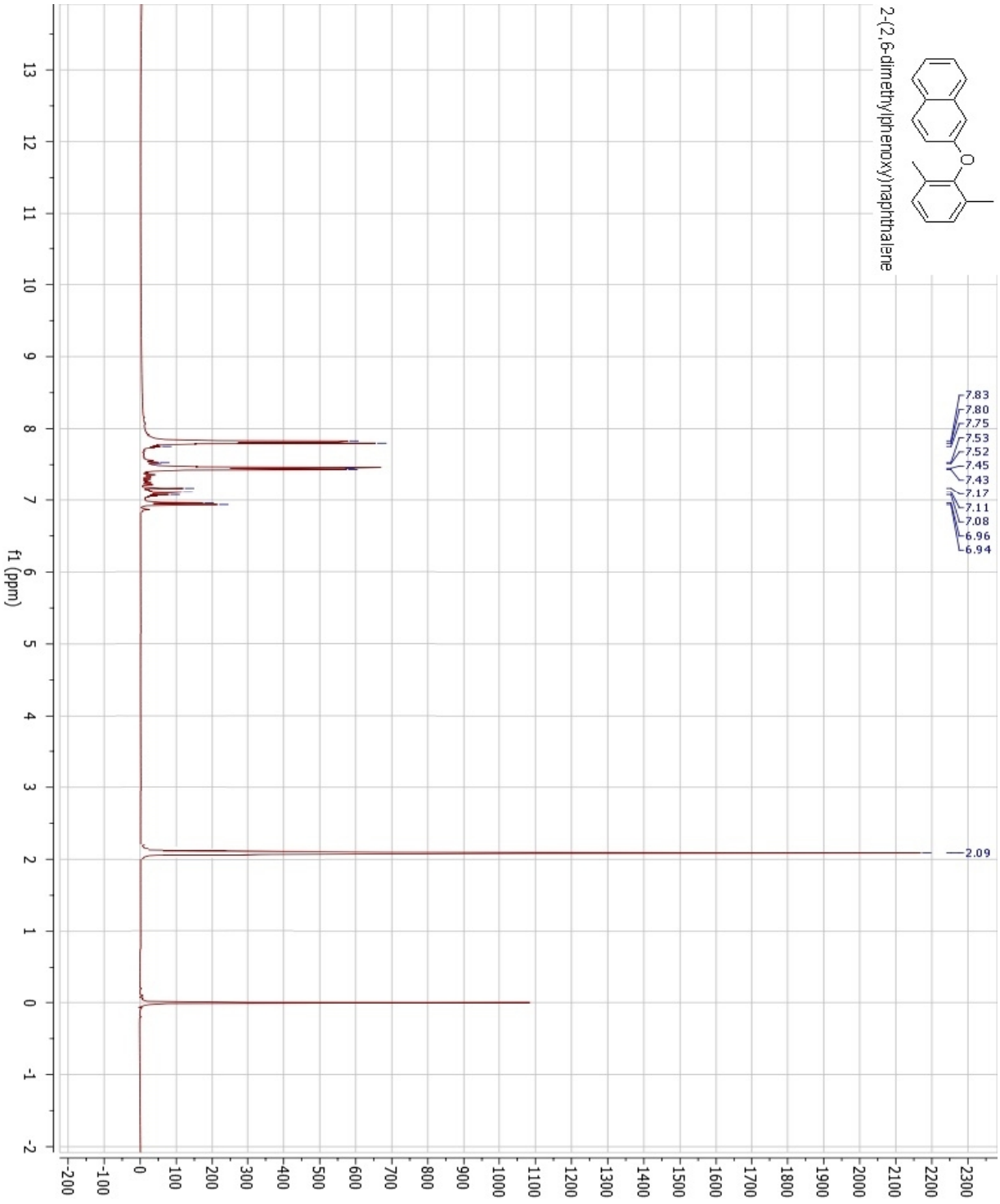

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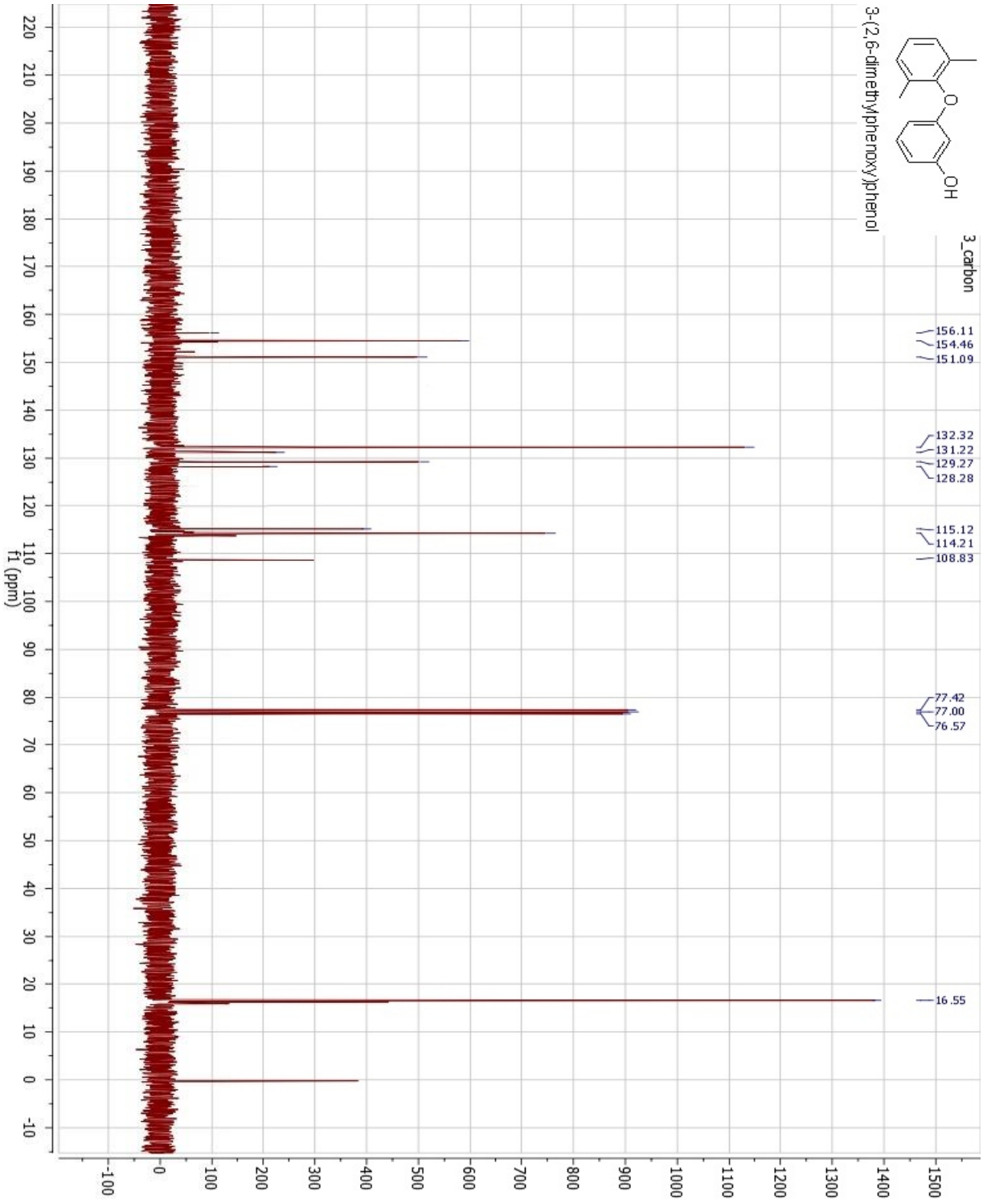

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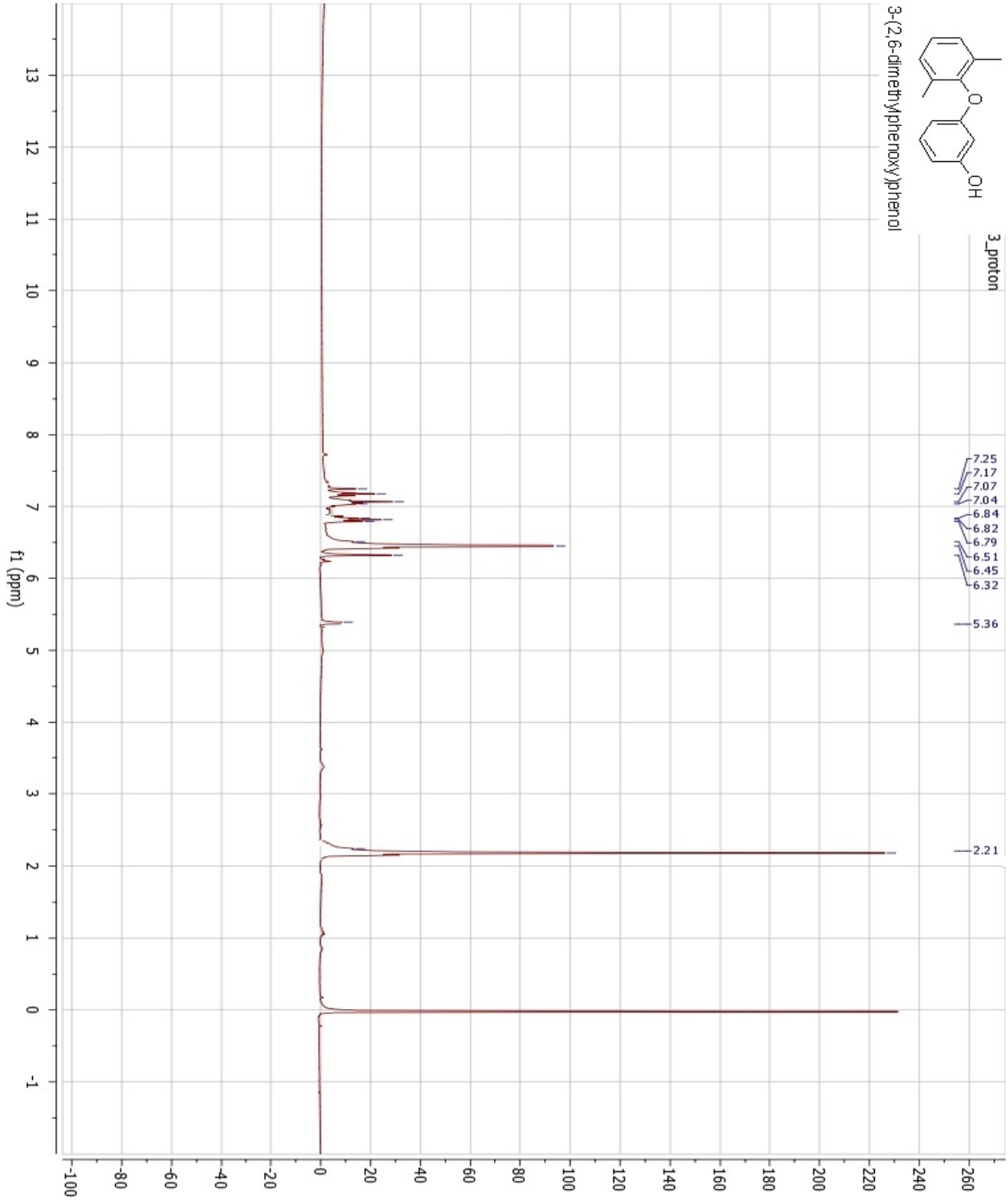

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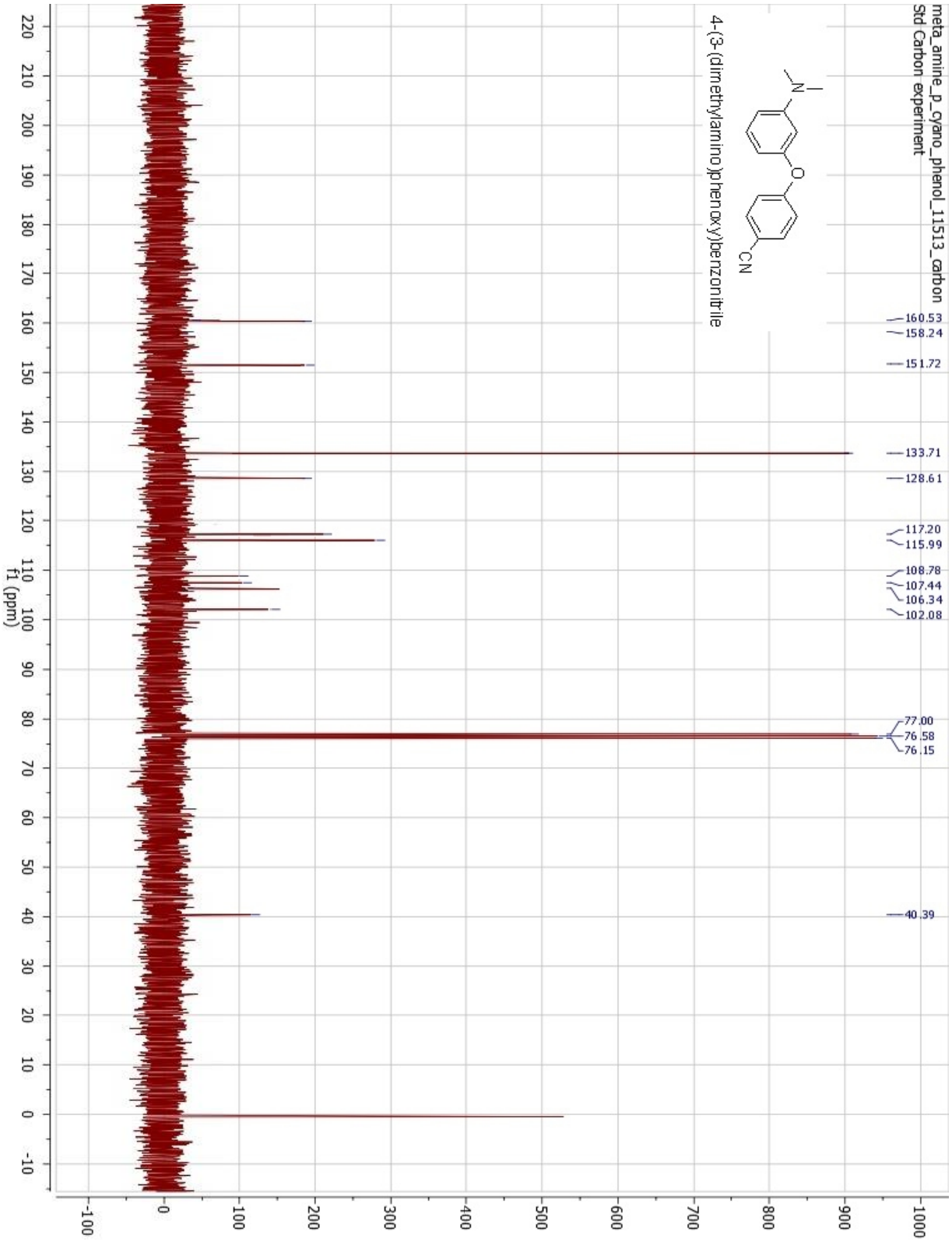

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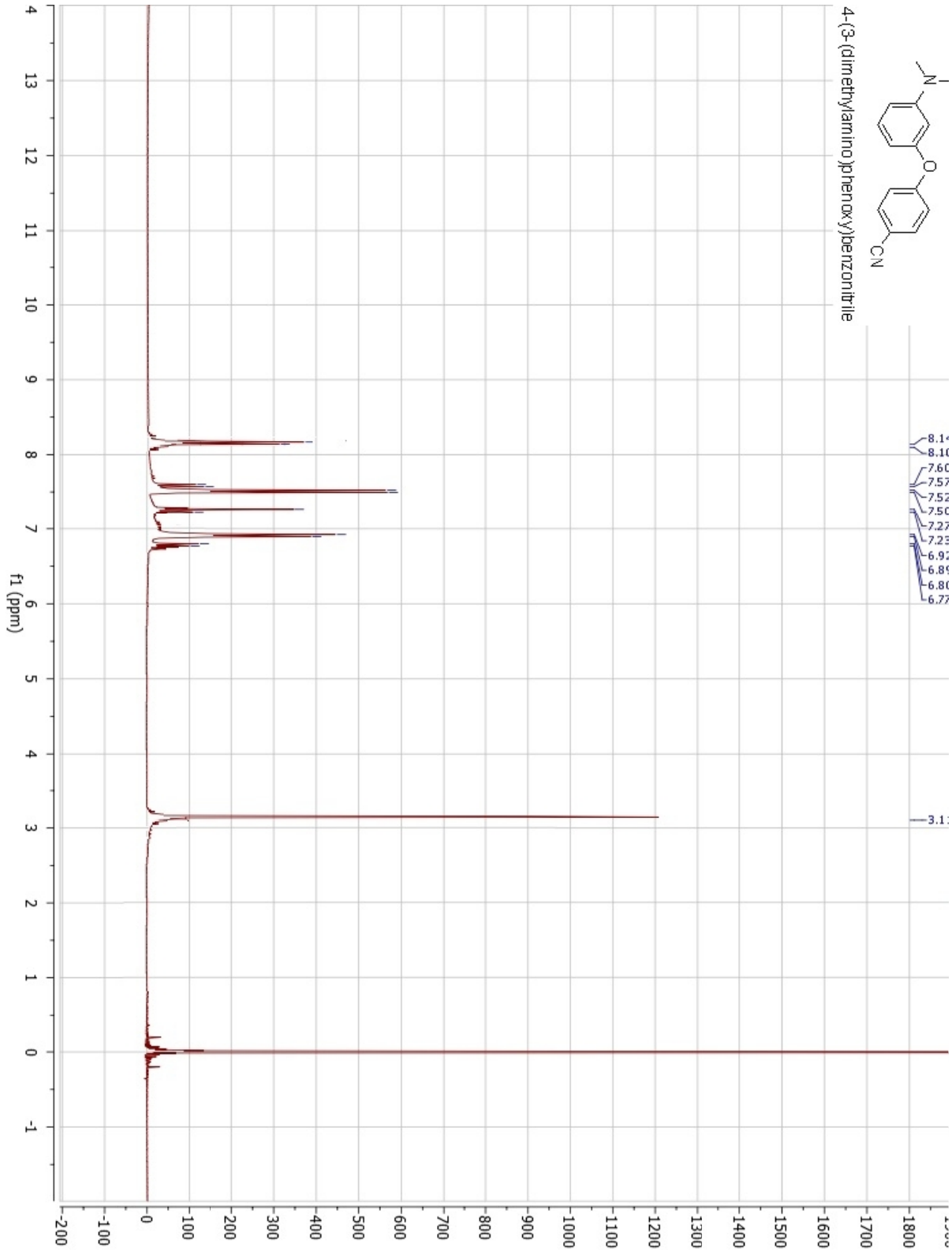

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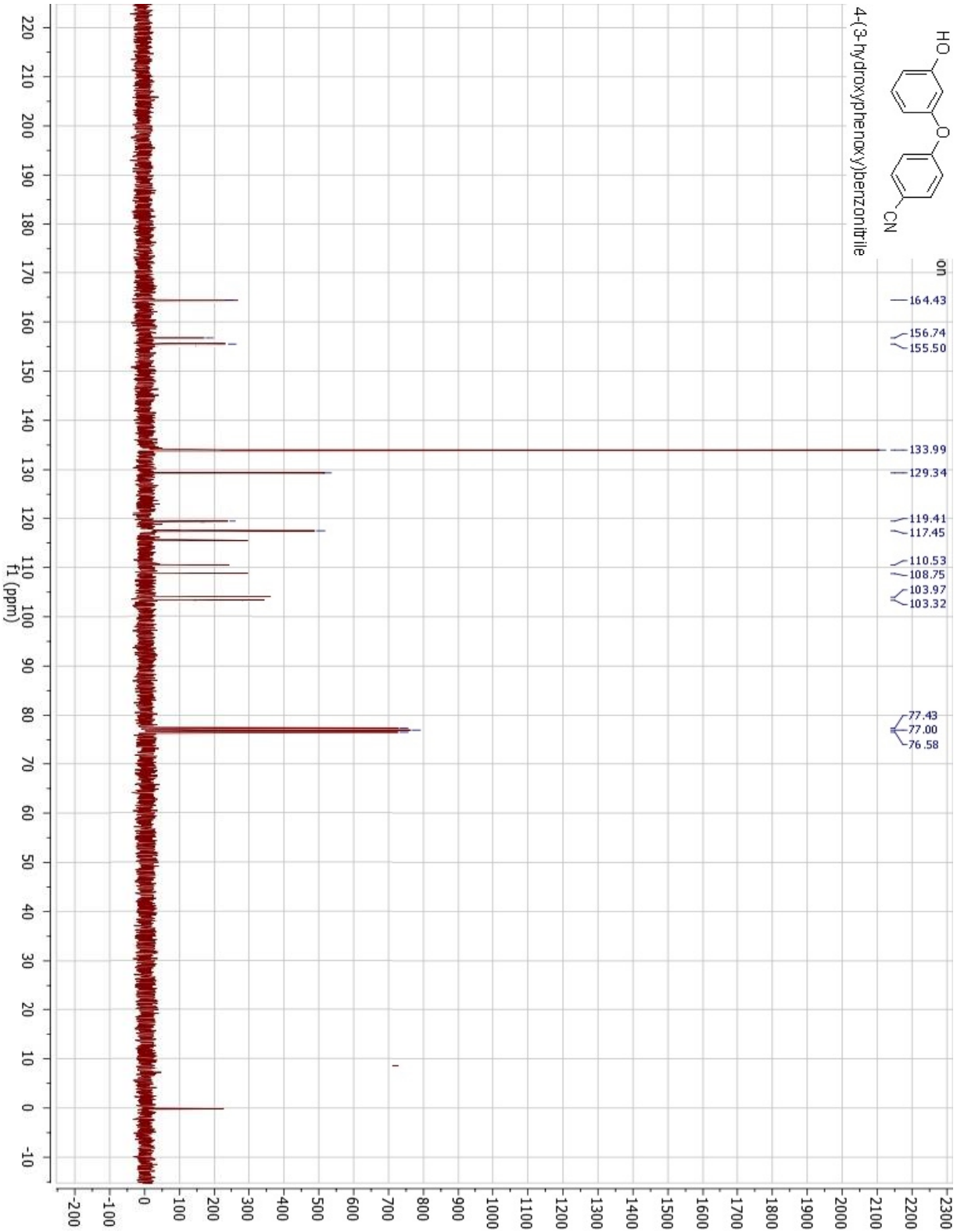

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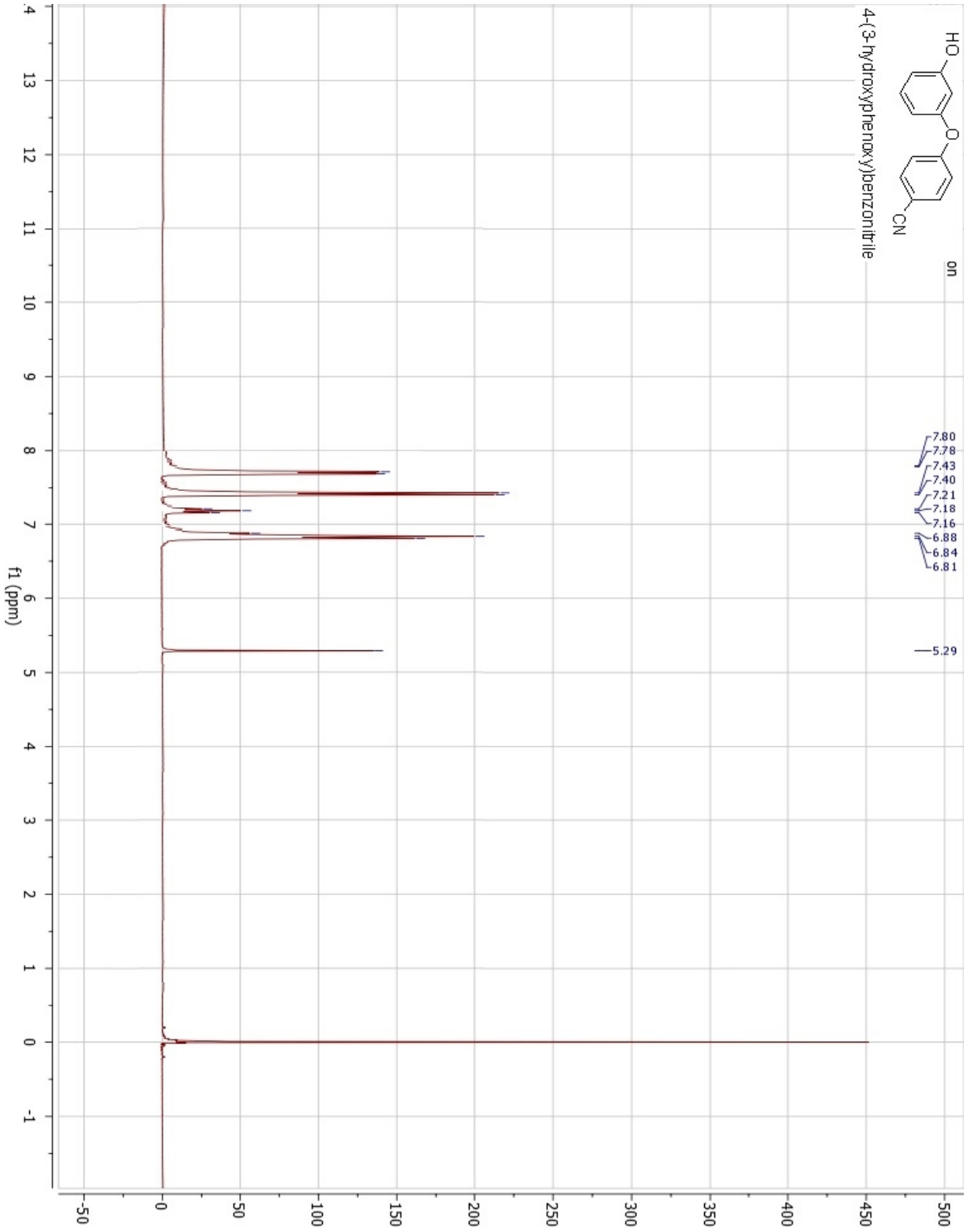

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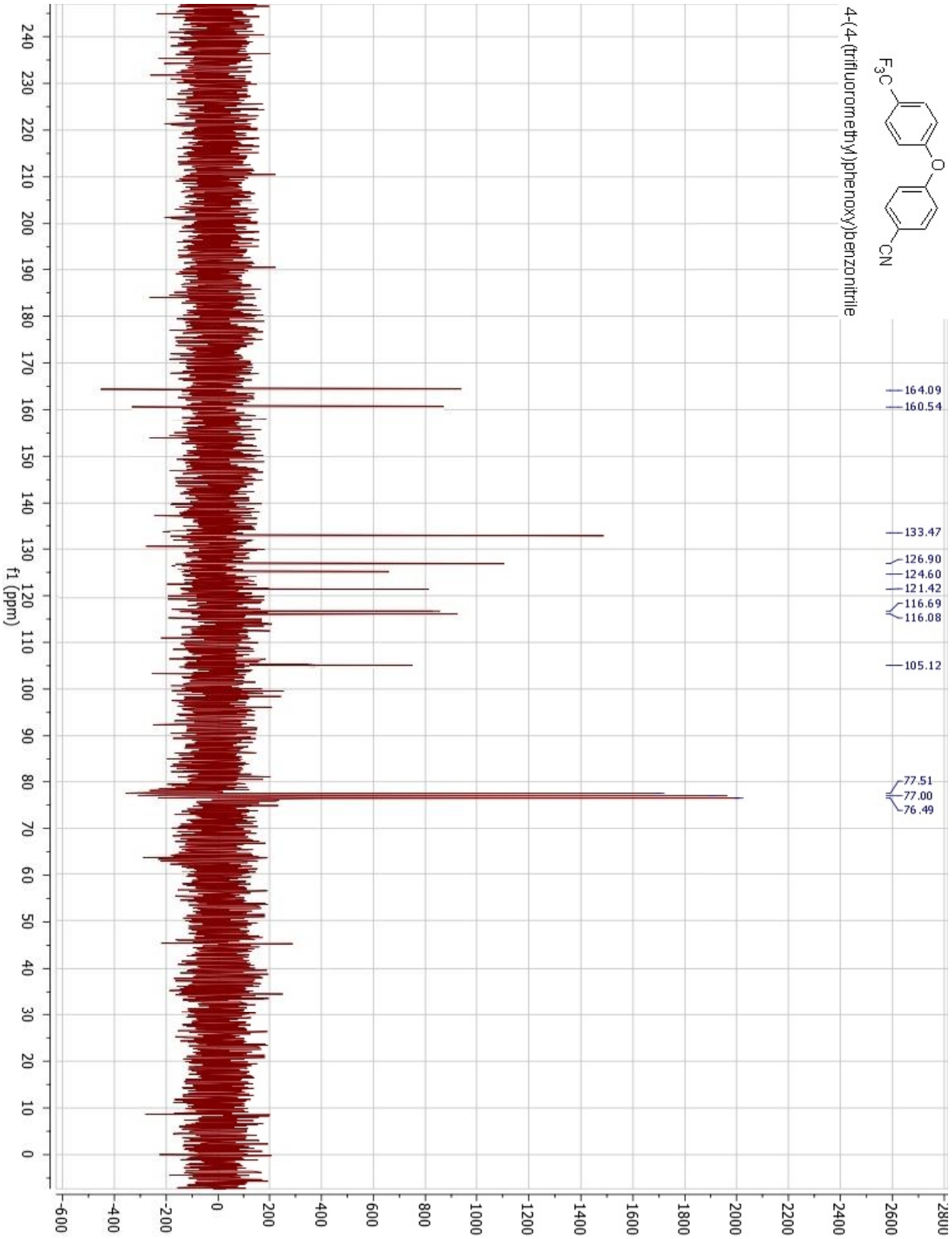

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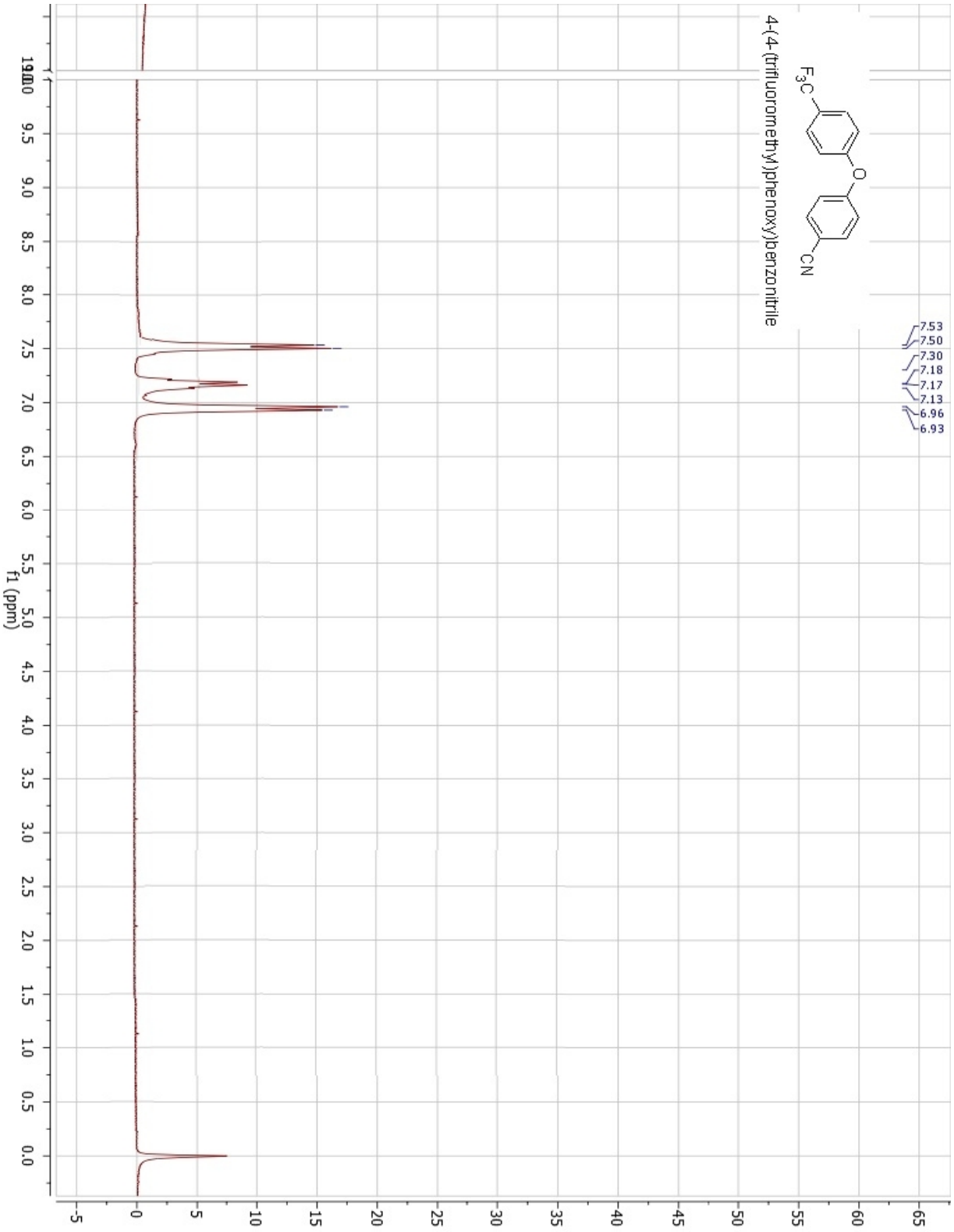

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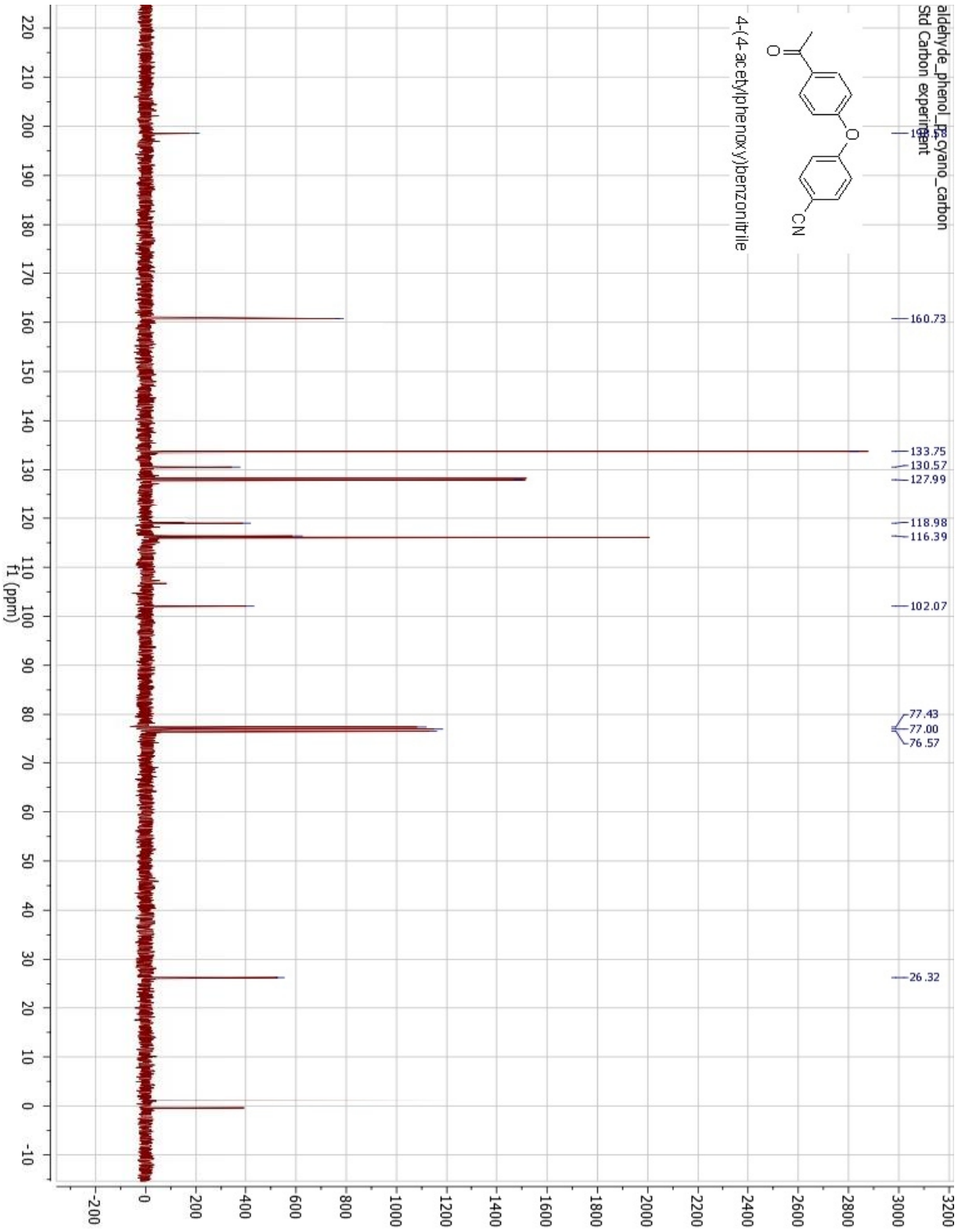

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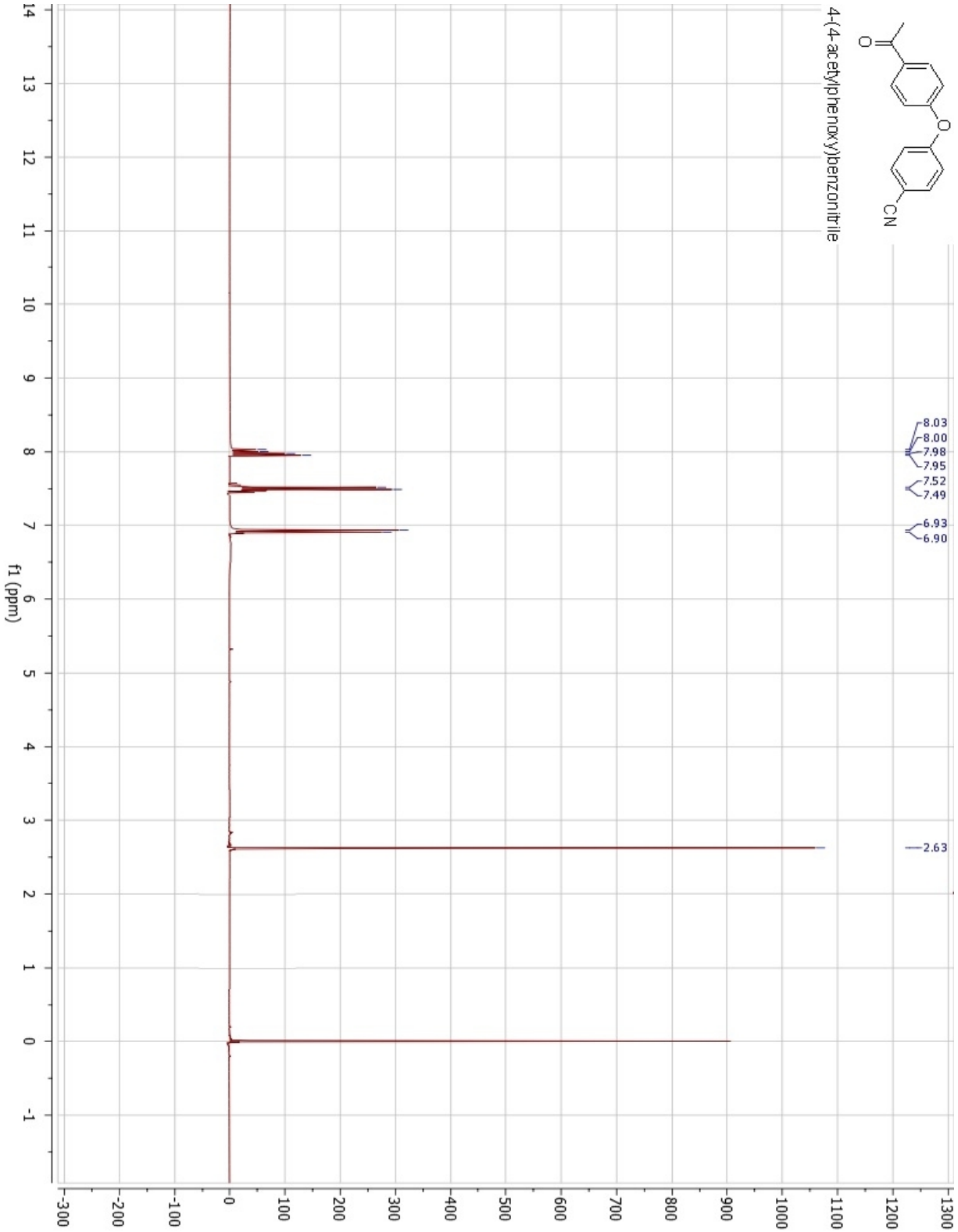

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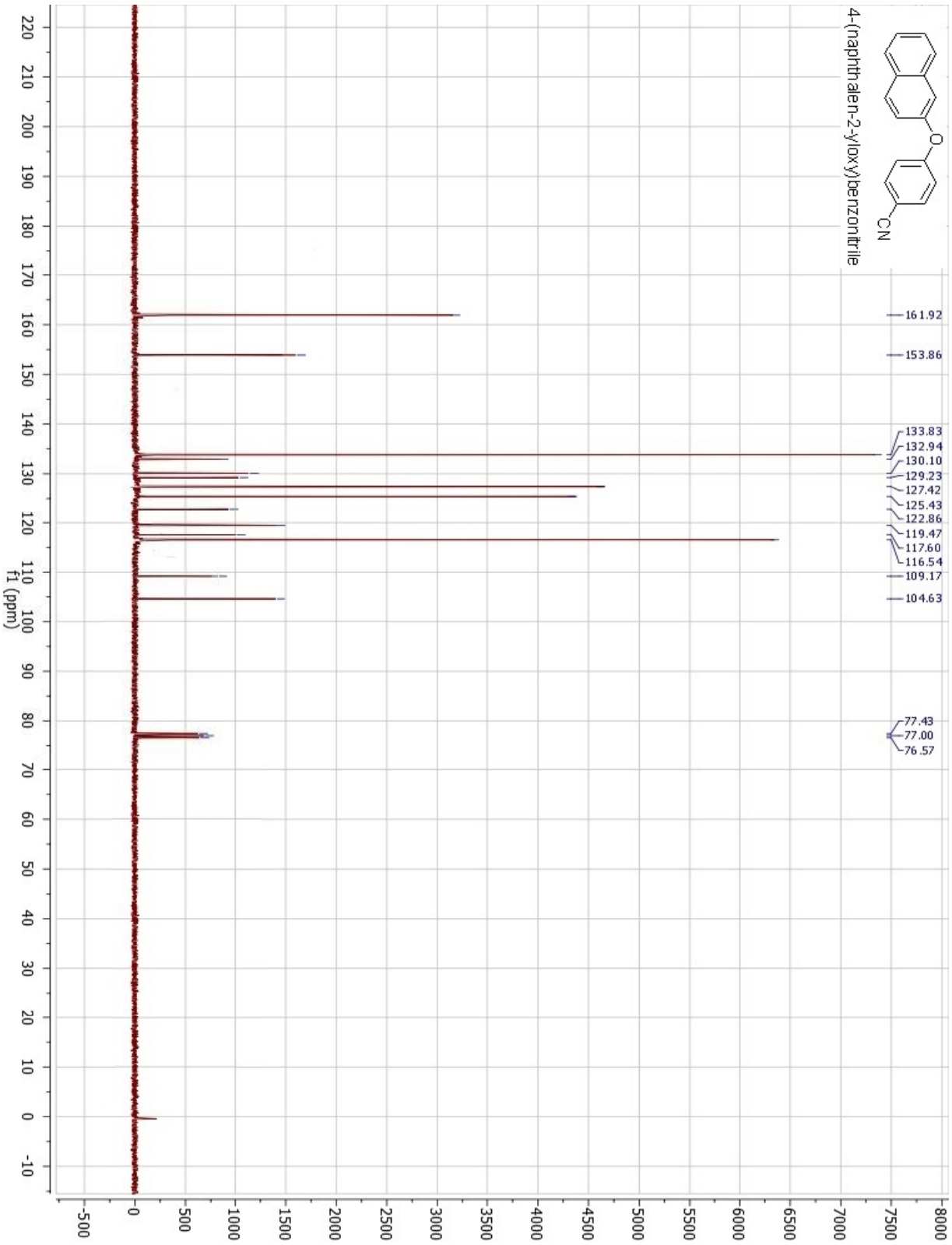

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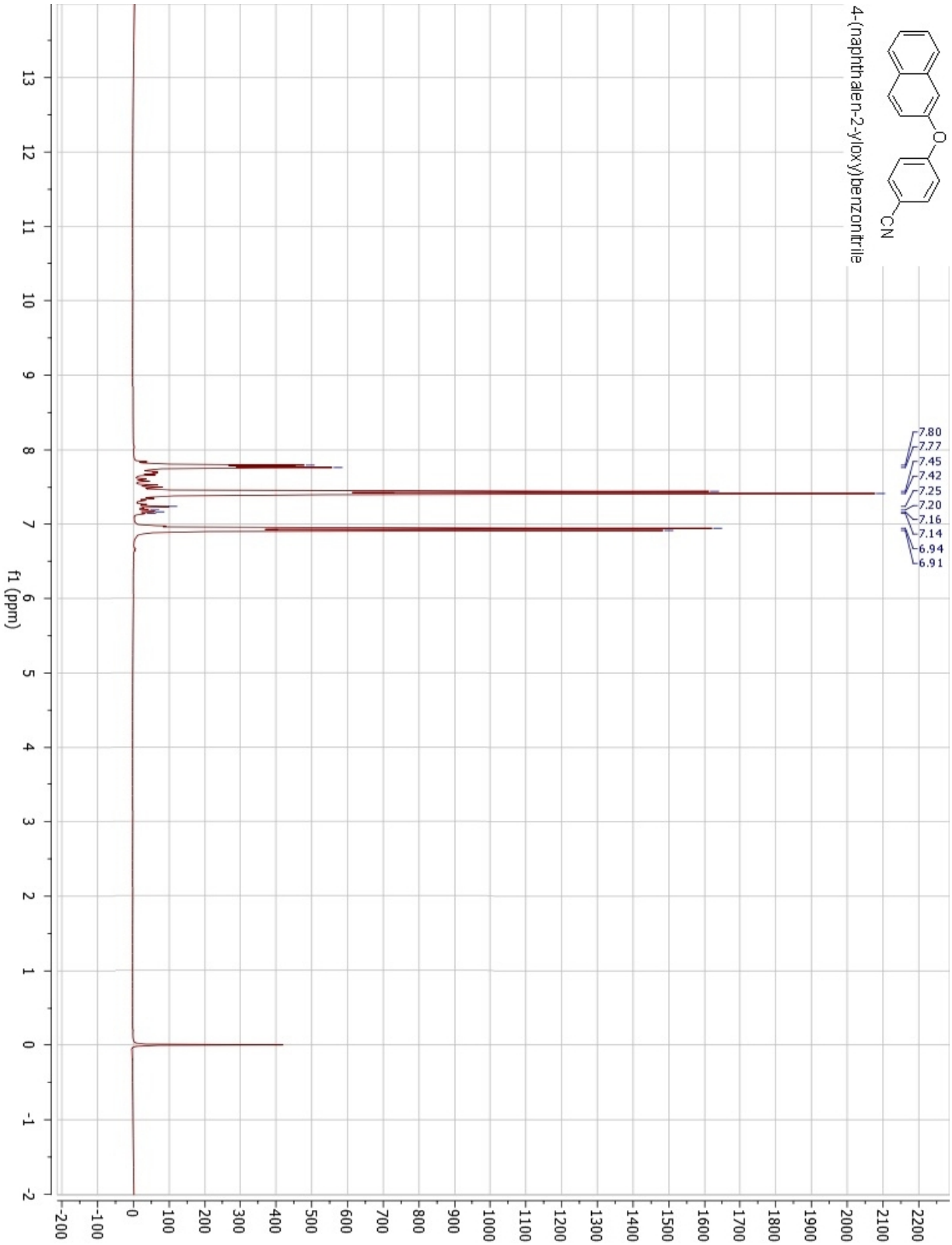

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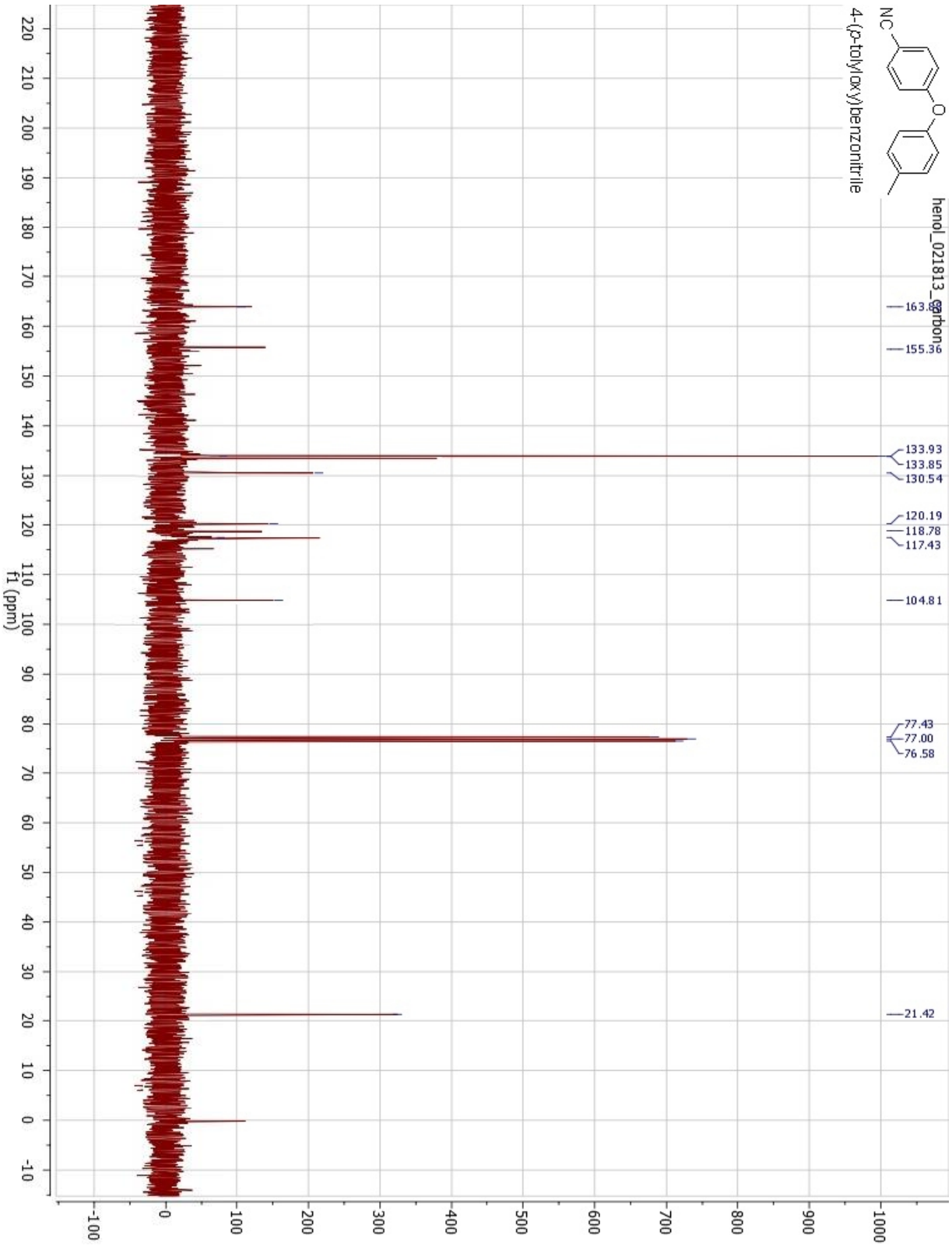

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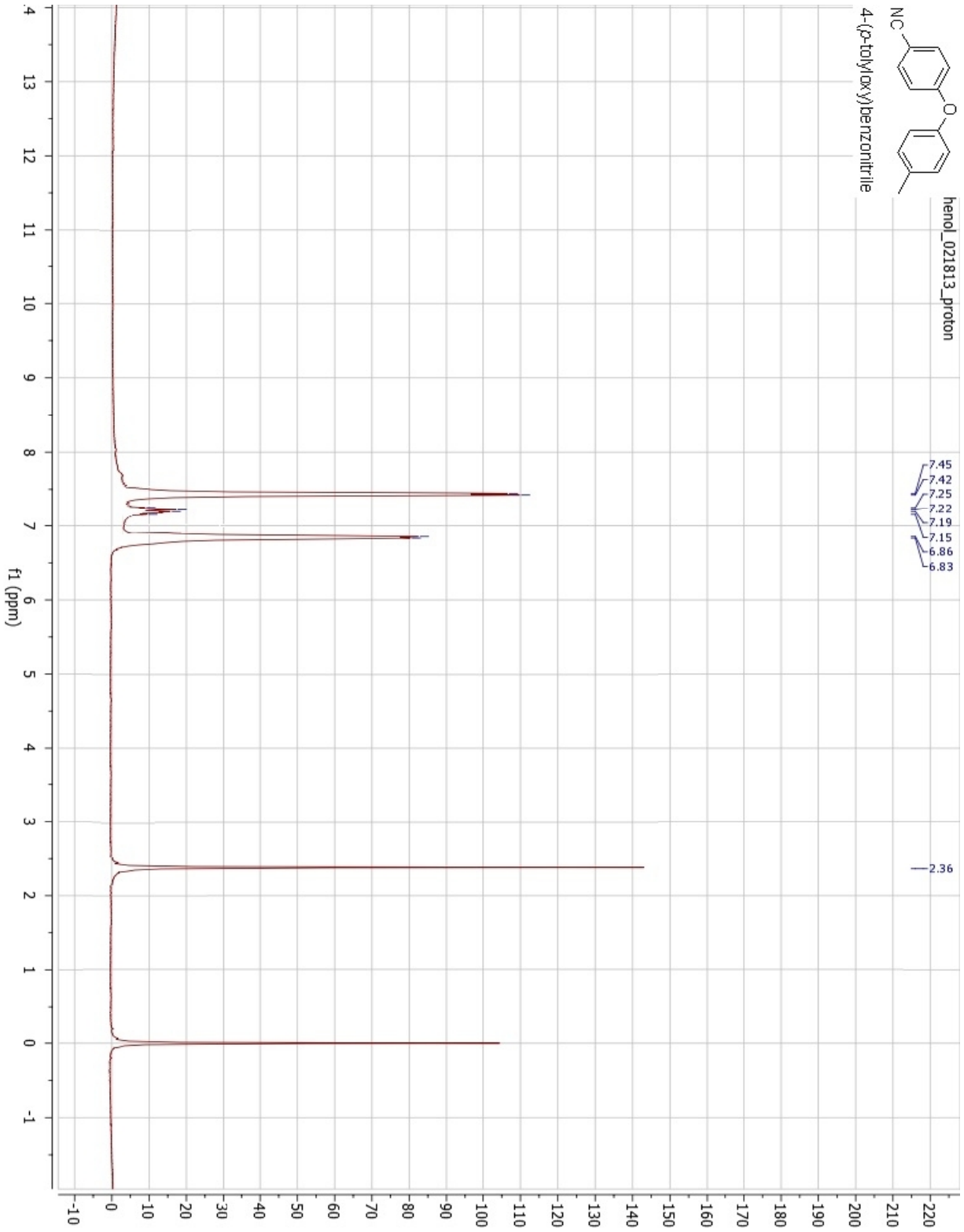

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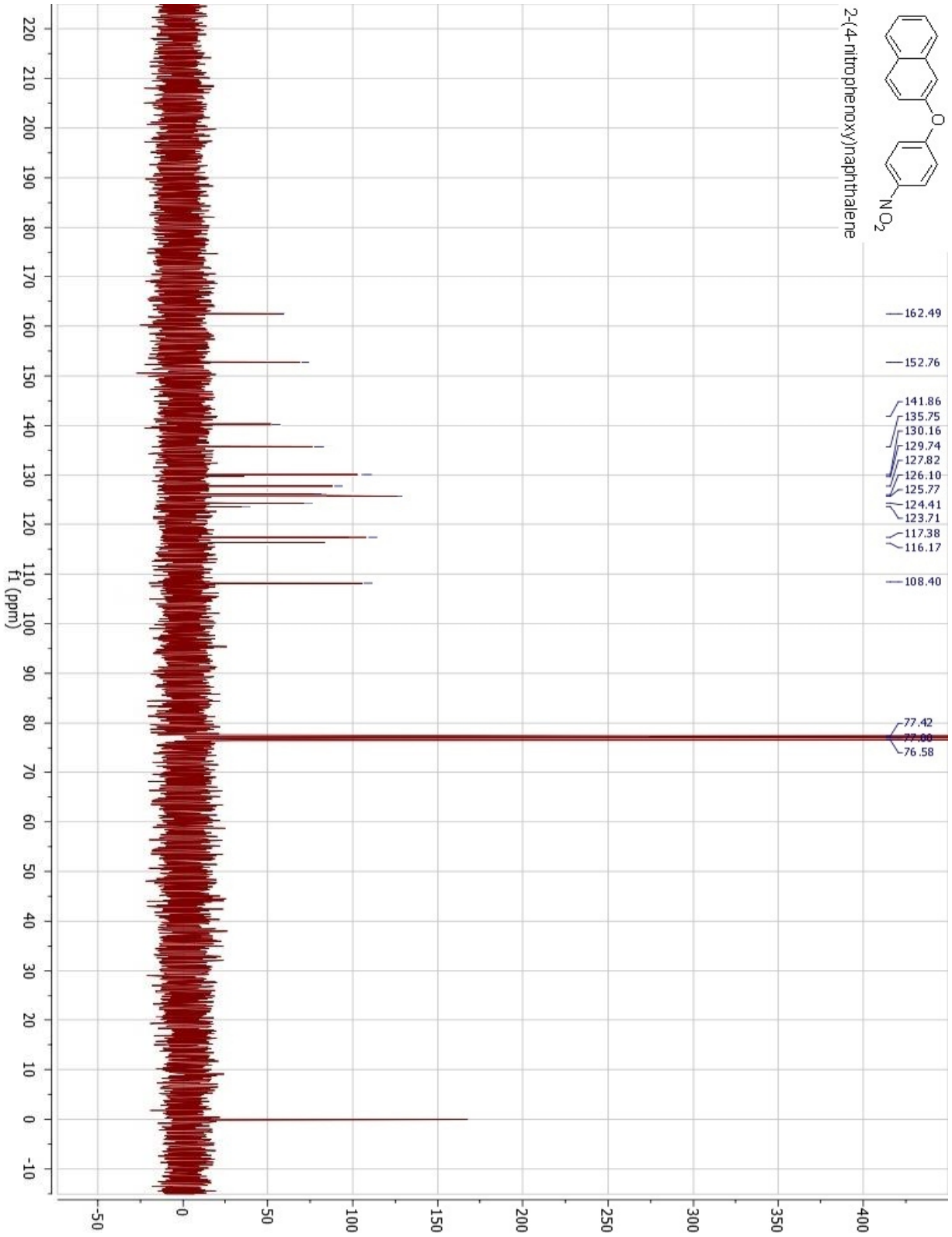

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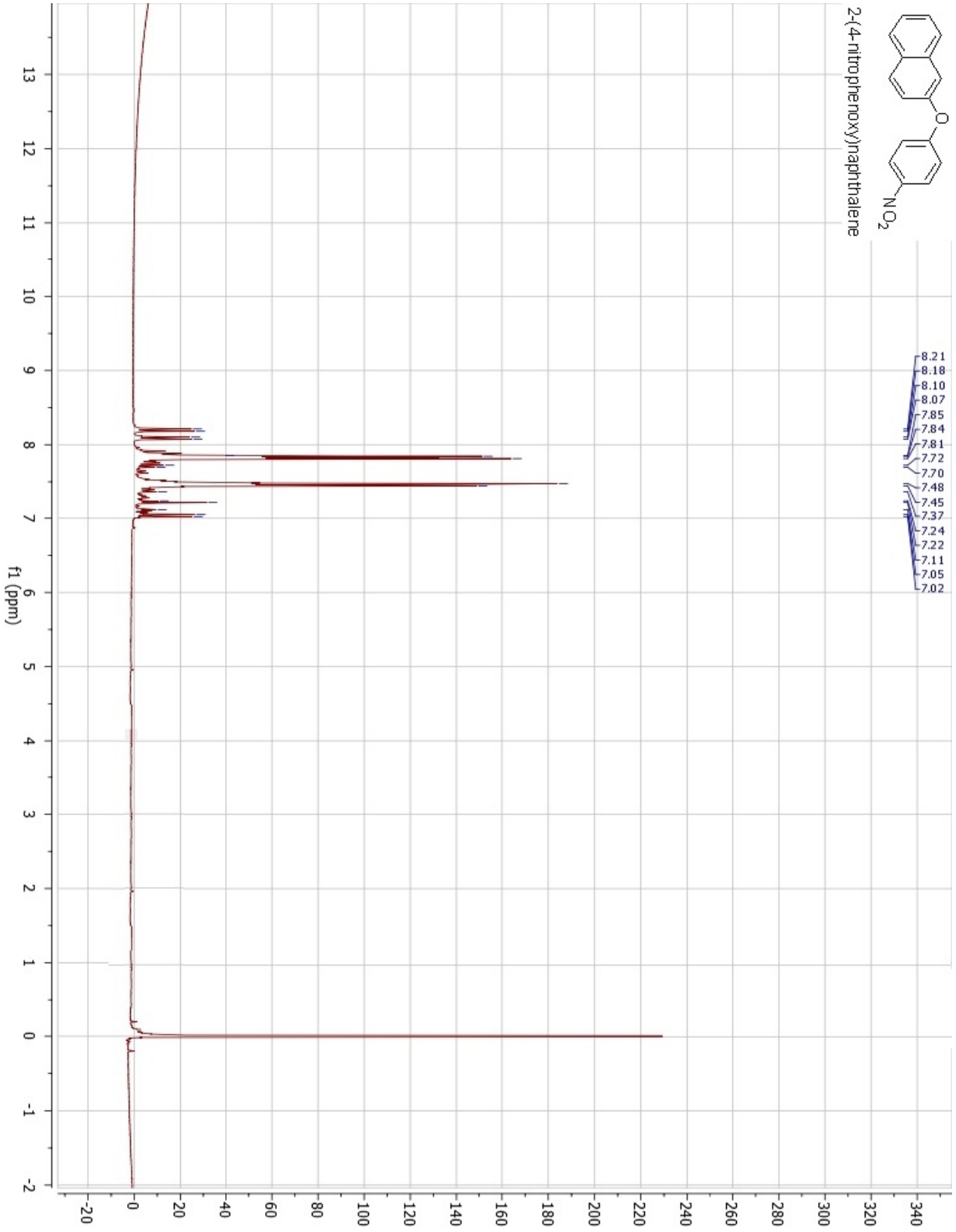

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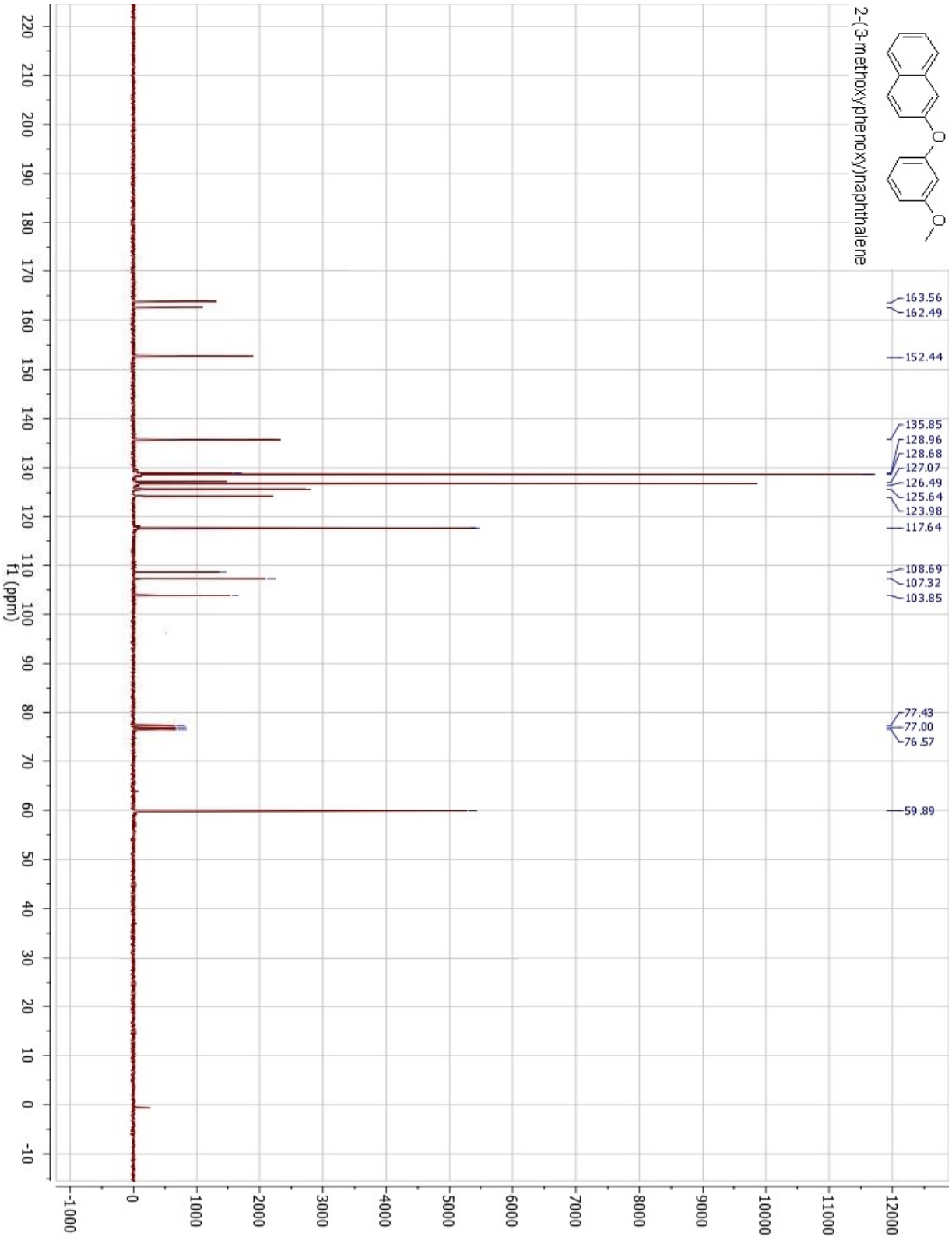

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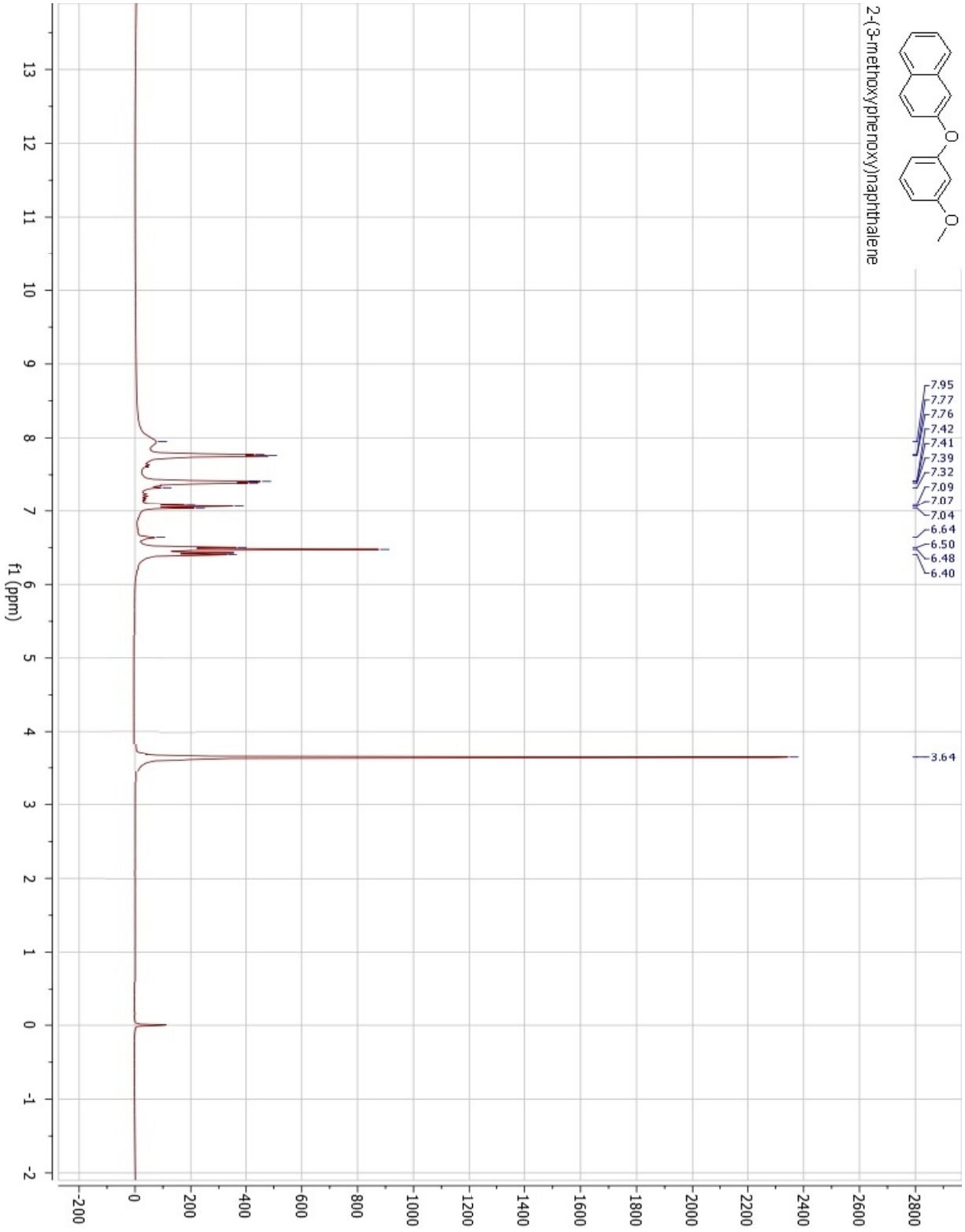

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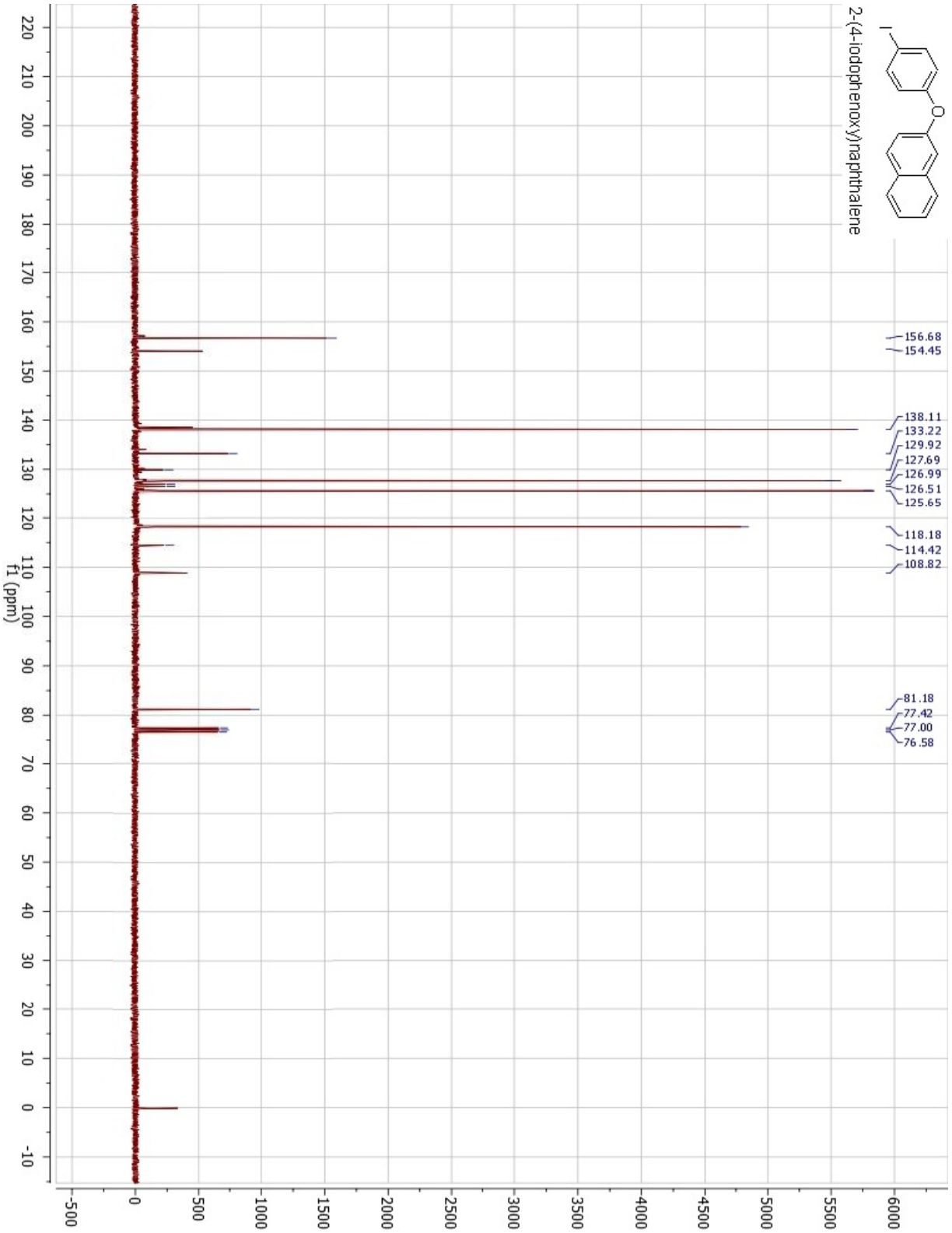

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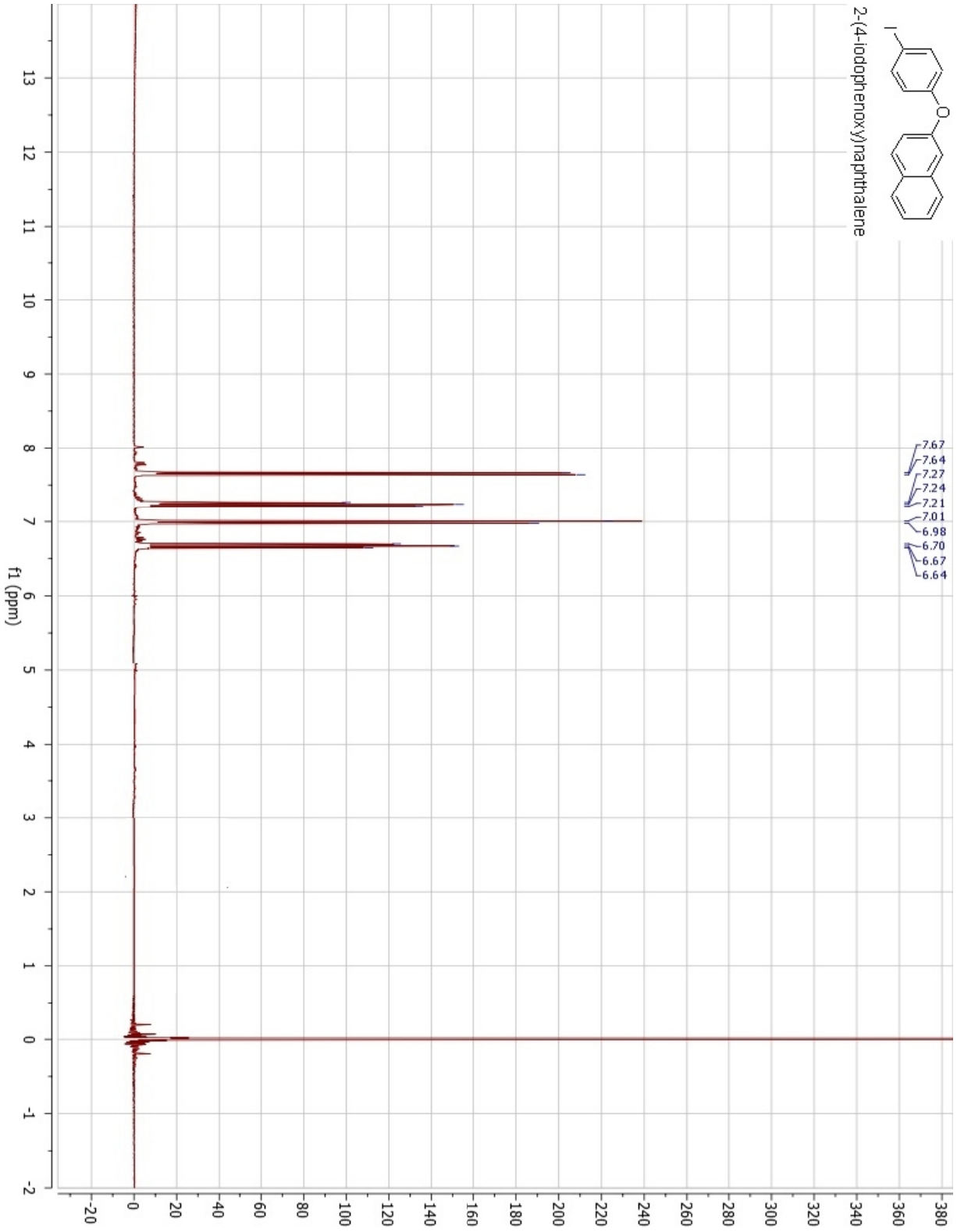

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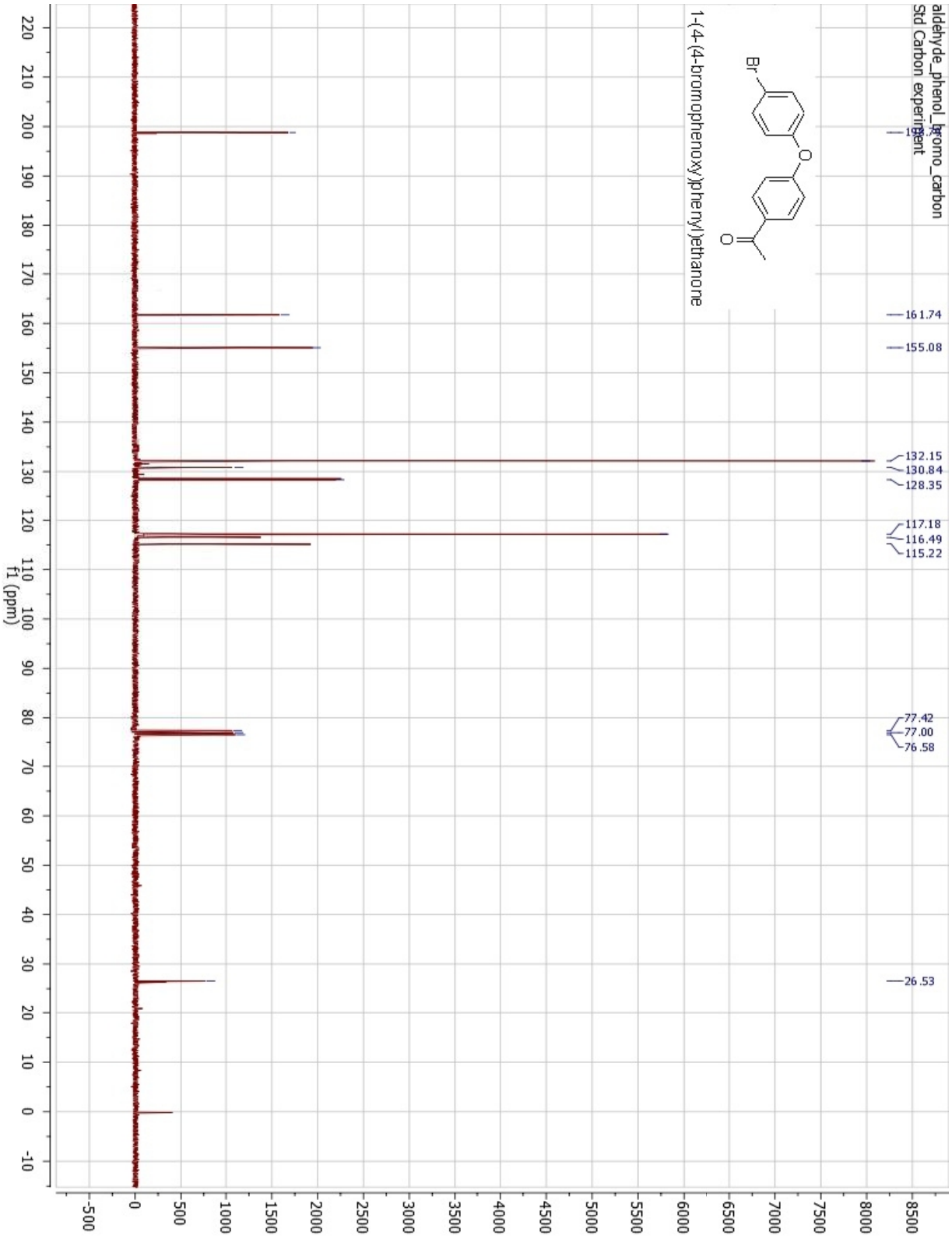

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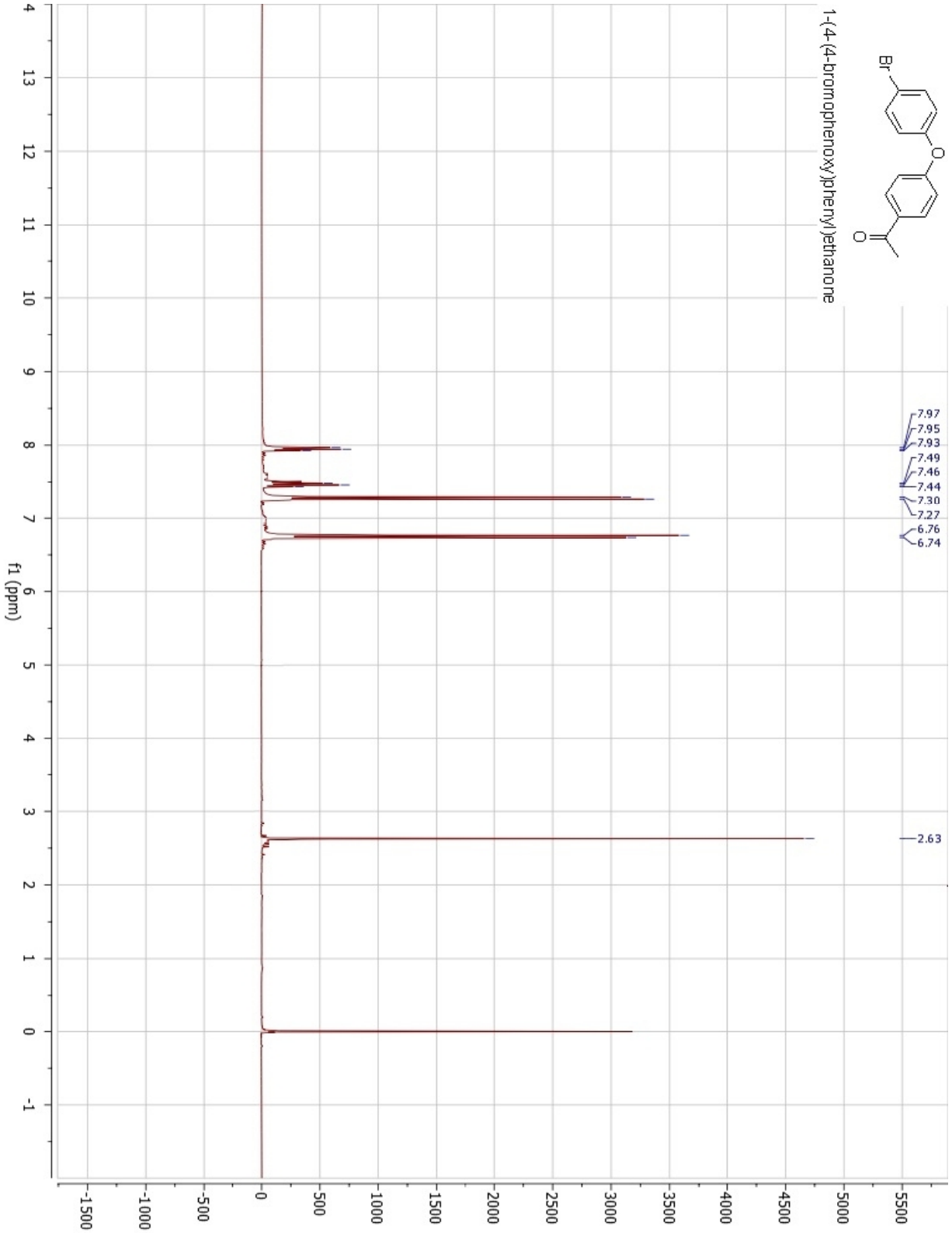

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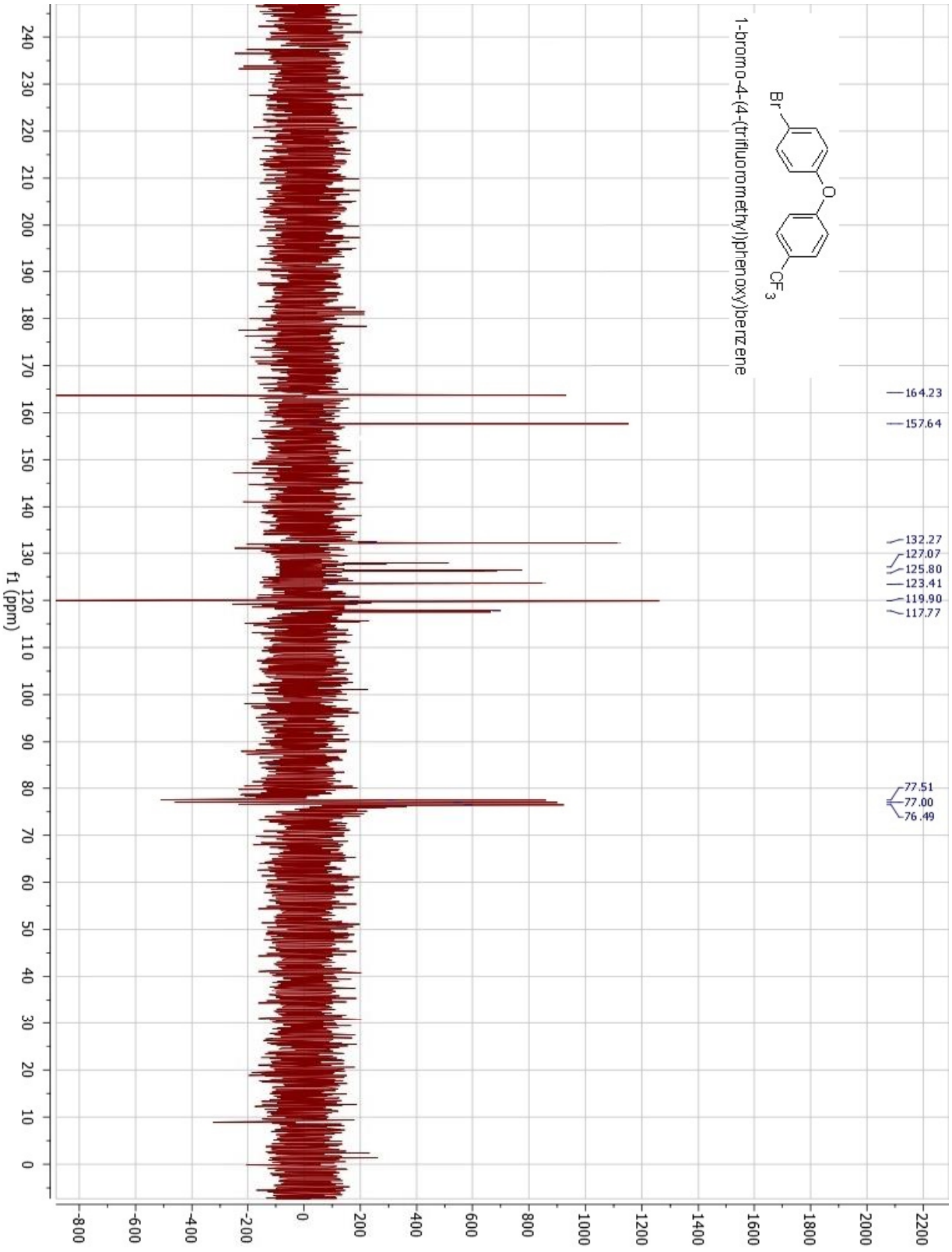

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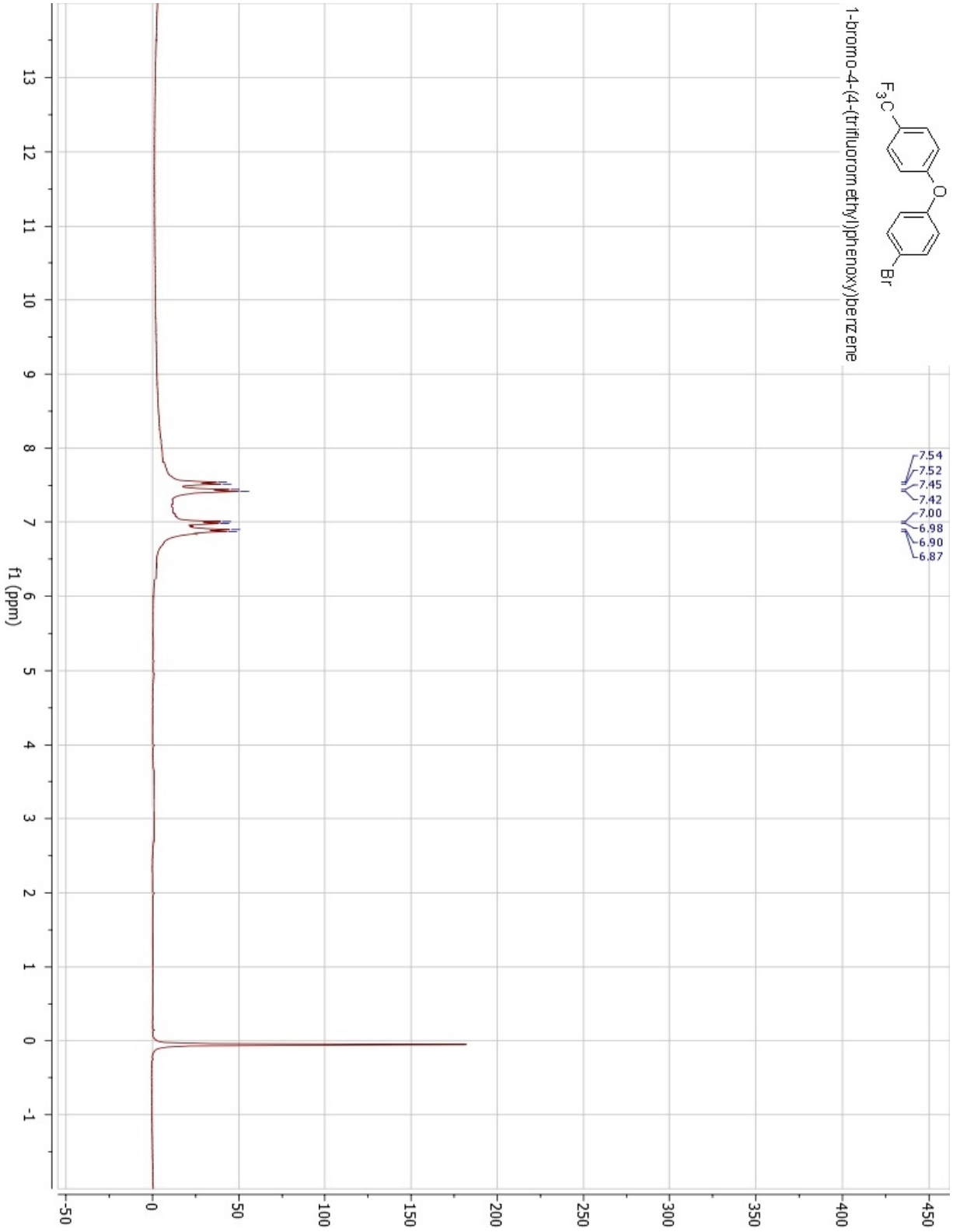

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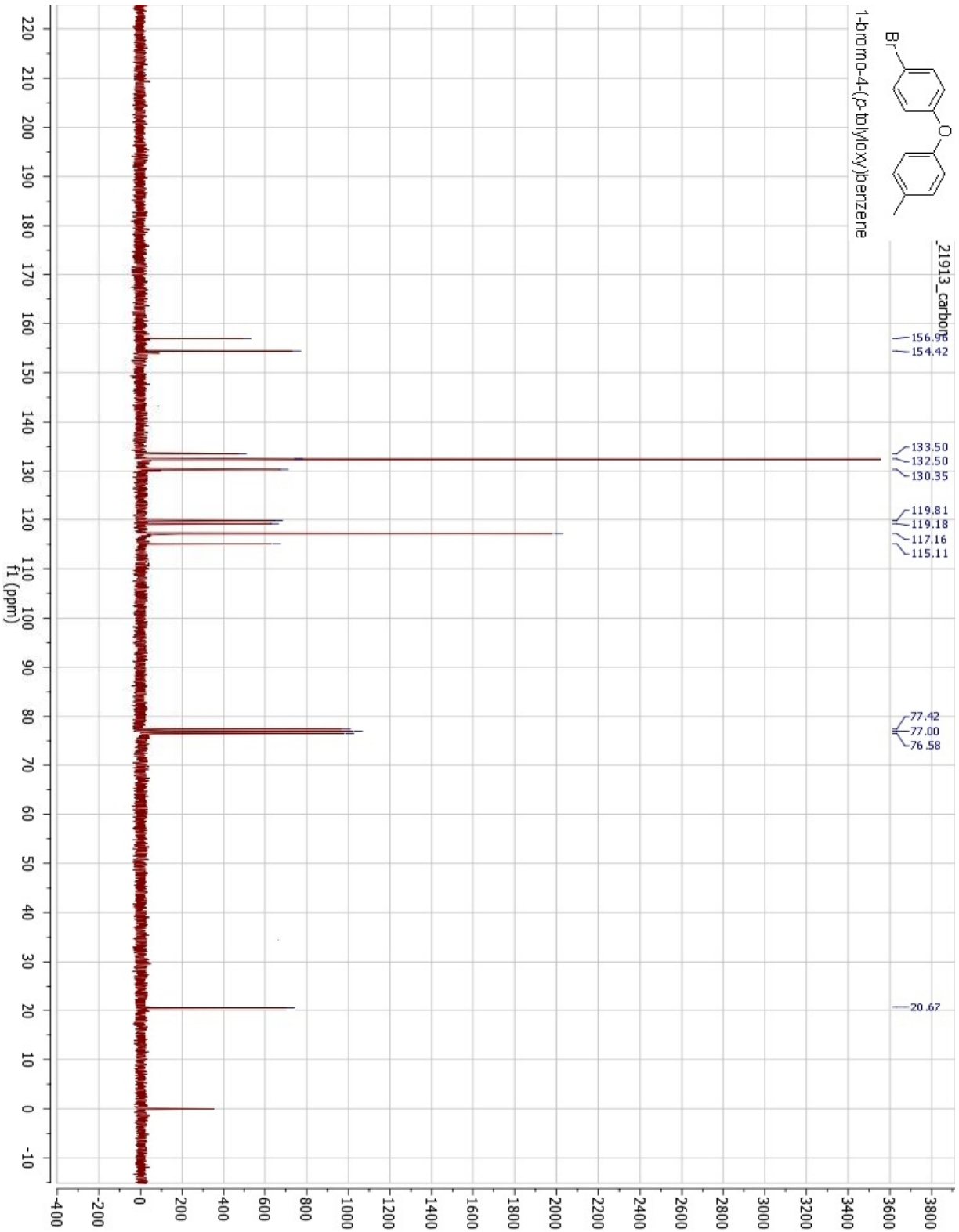

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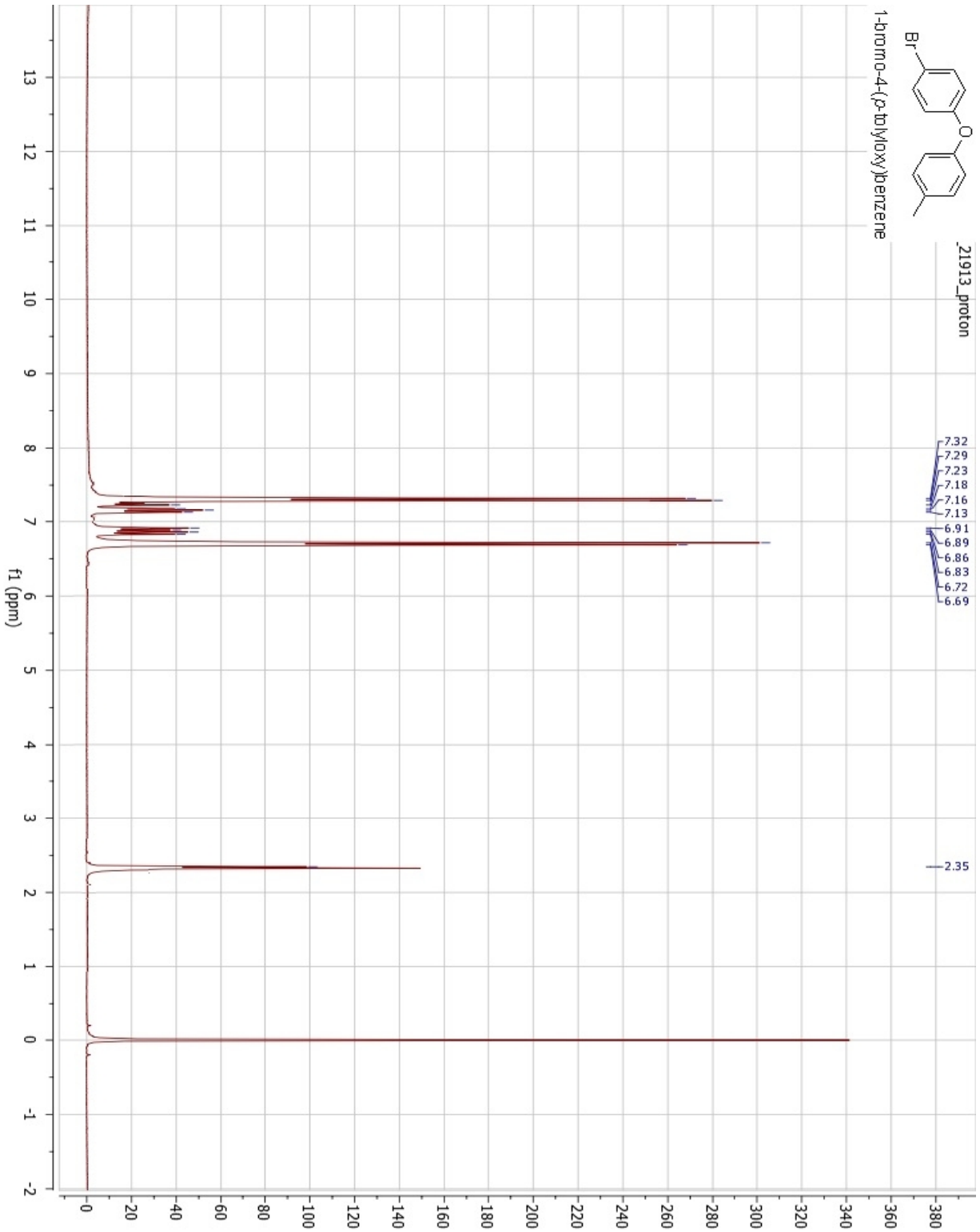

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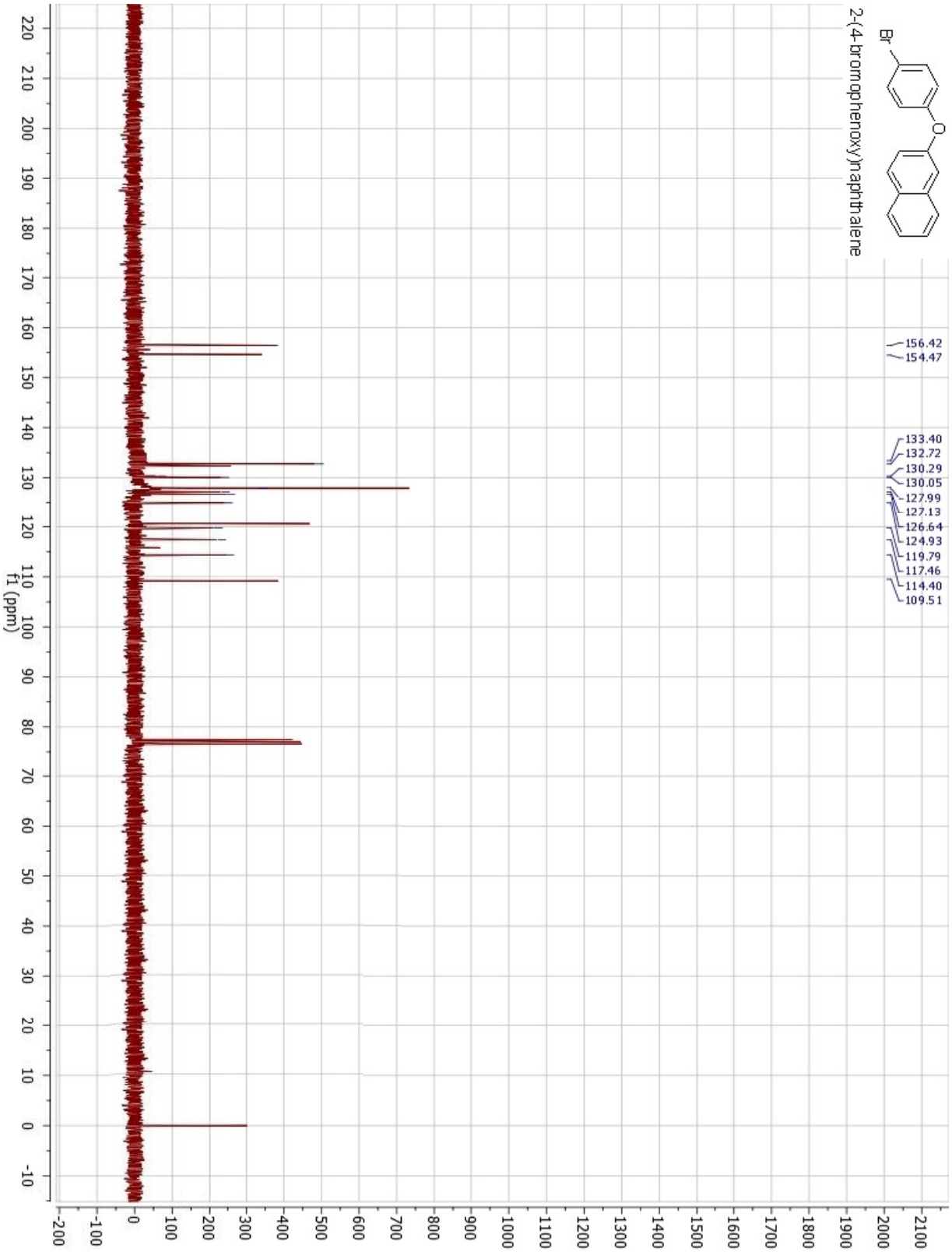

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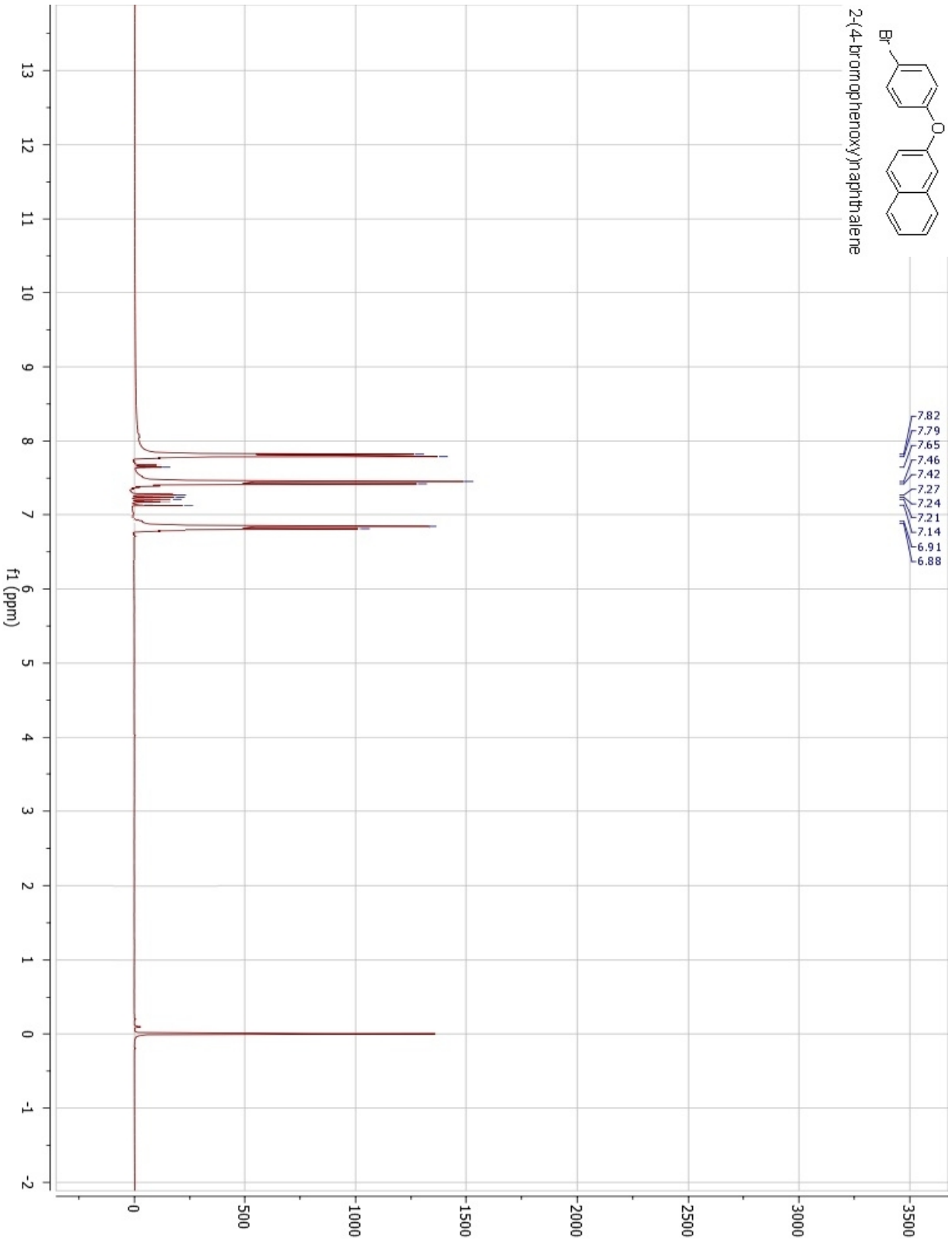

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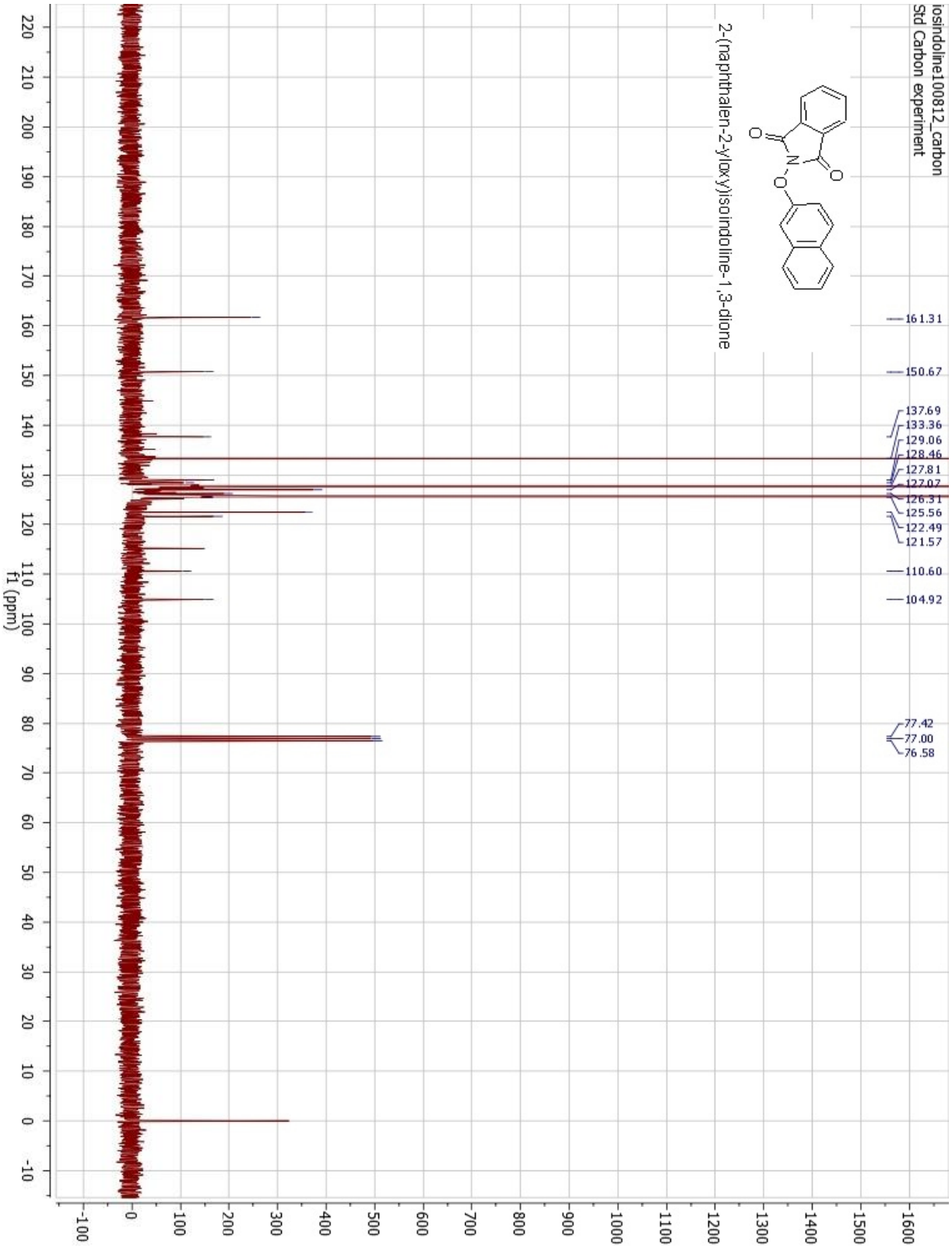
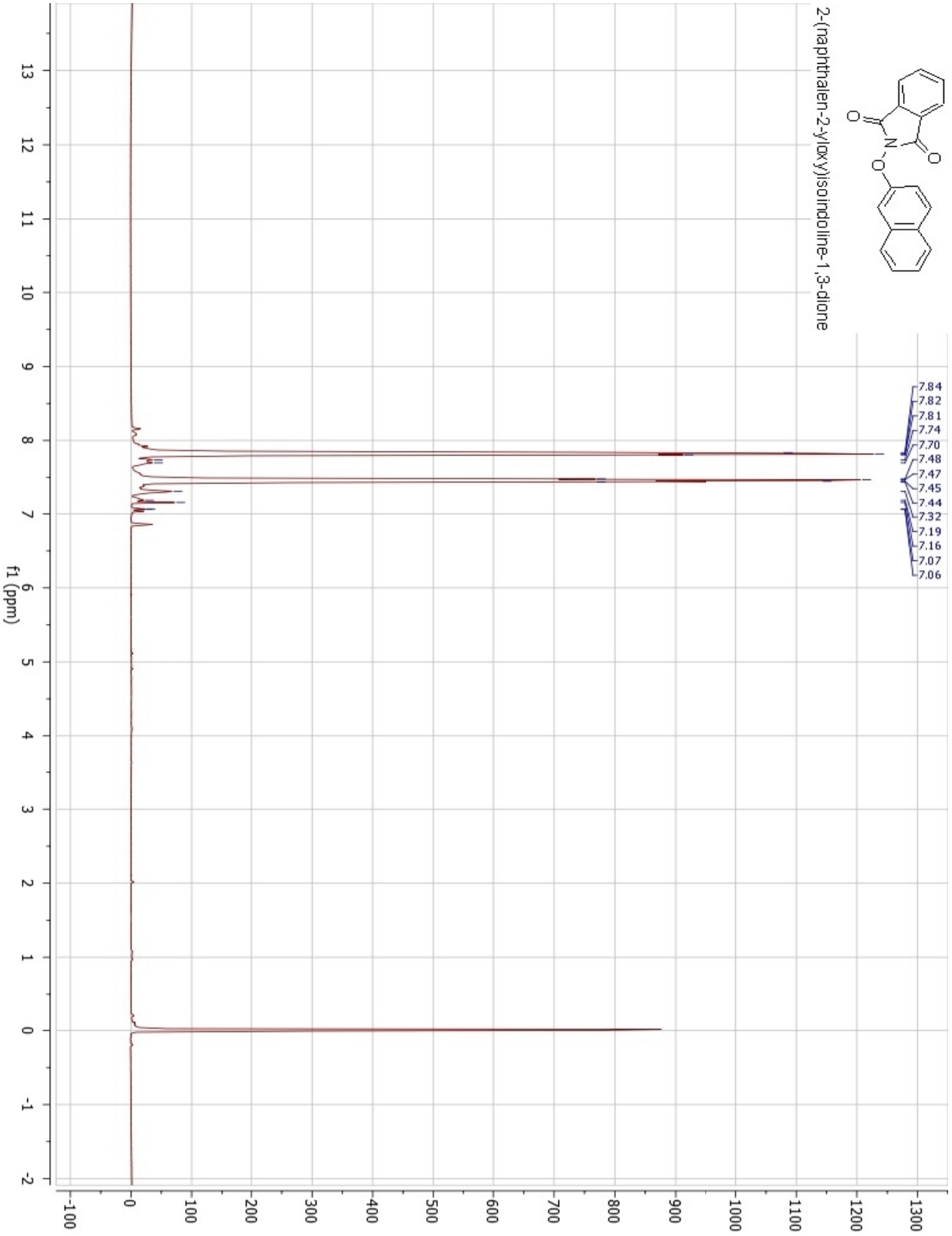
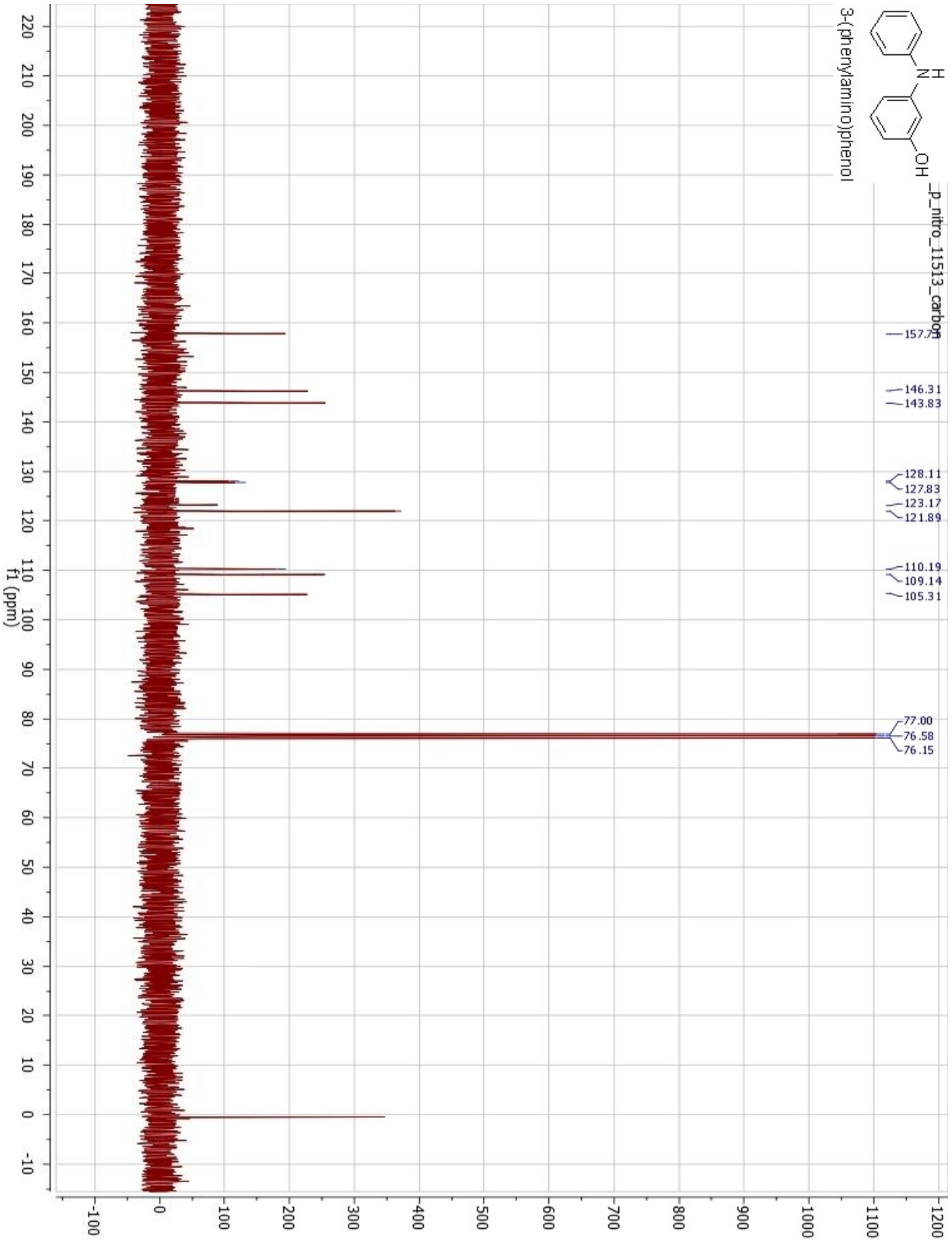


[1]Hydrogen NMR



^{13}Carbon NMR



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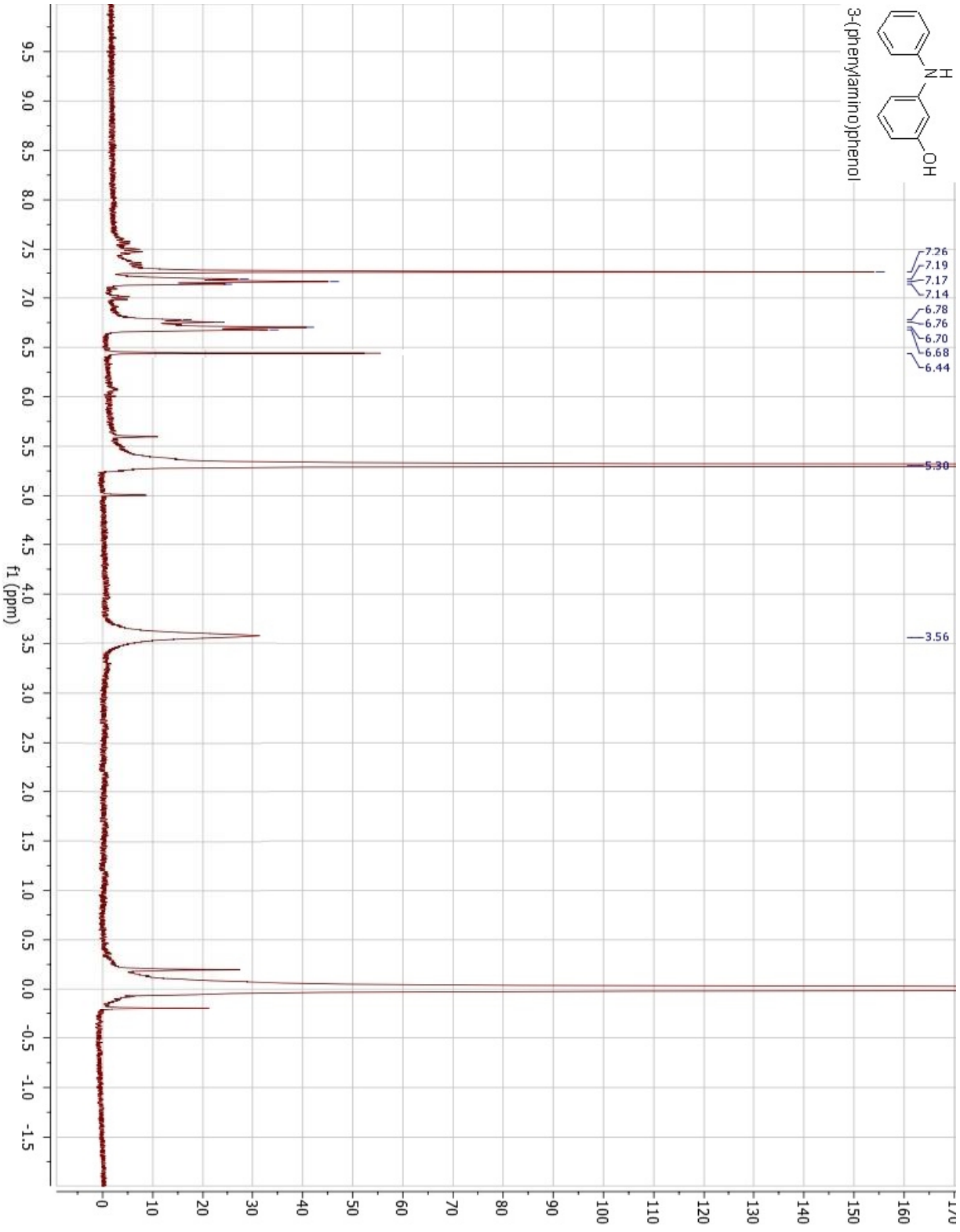

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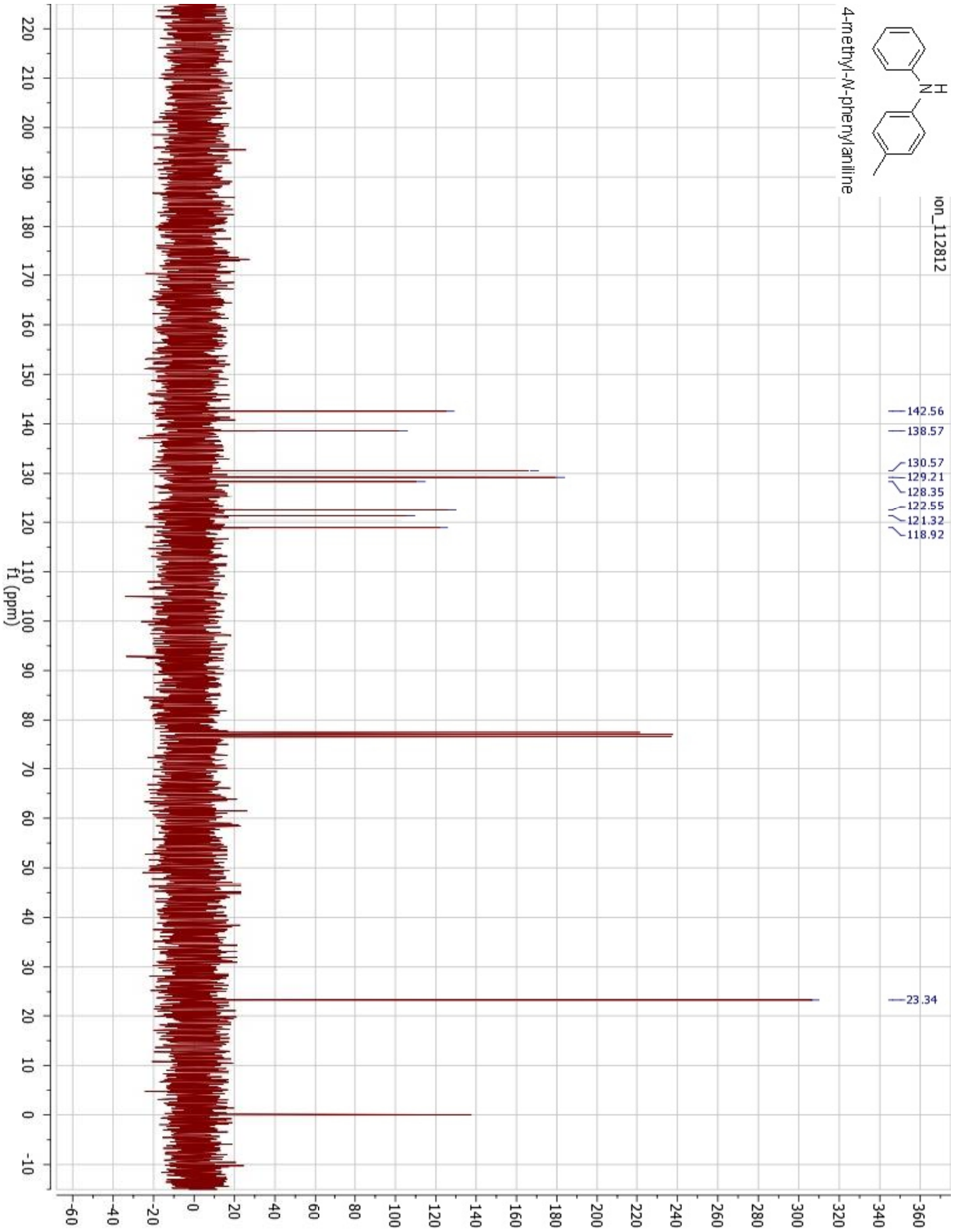

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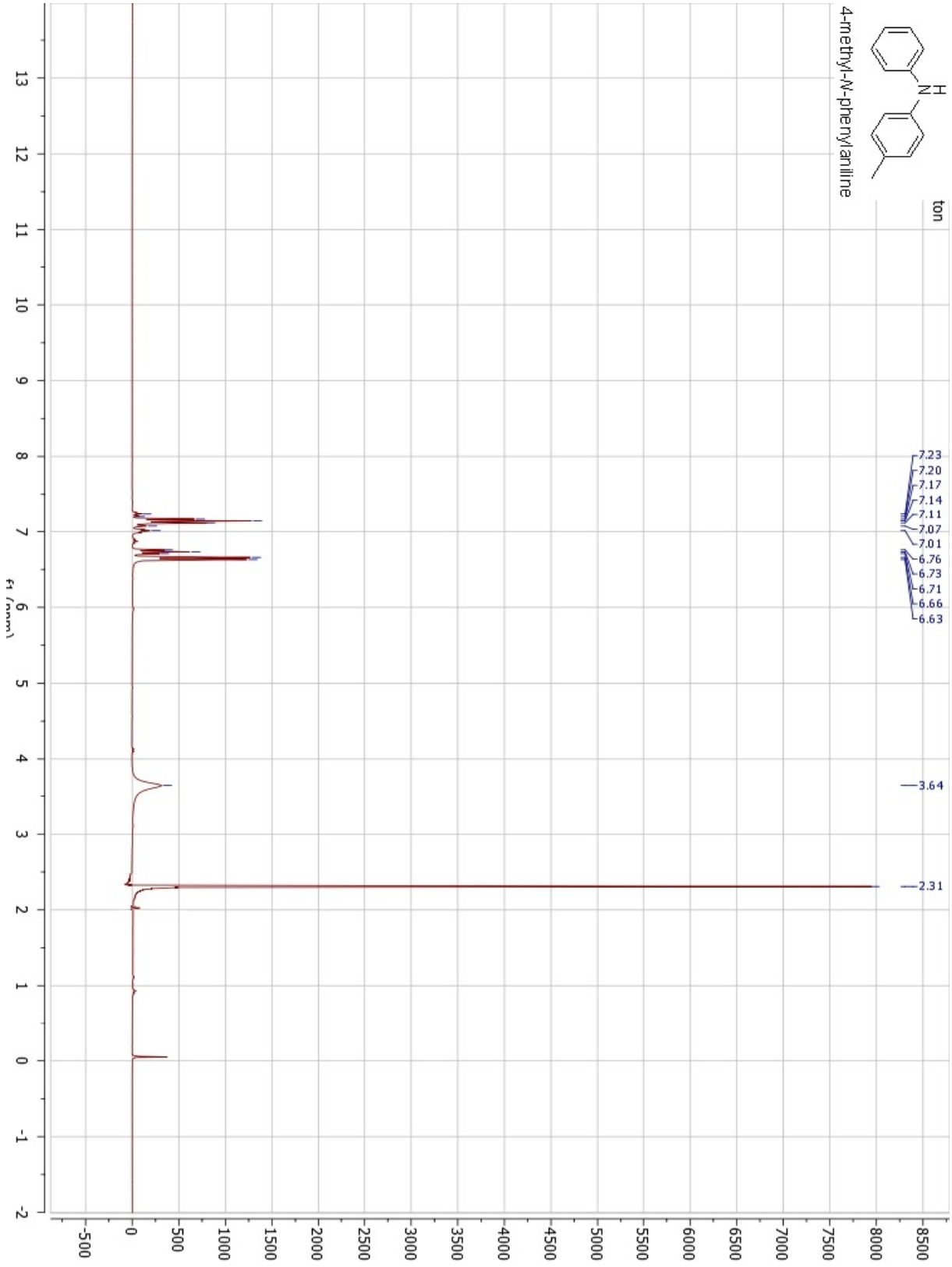

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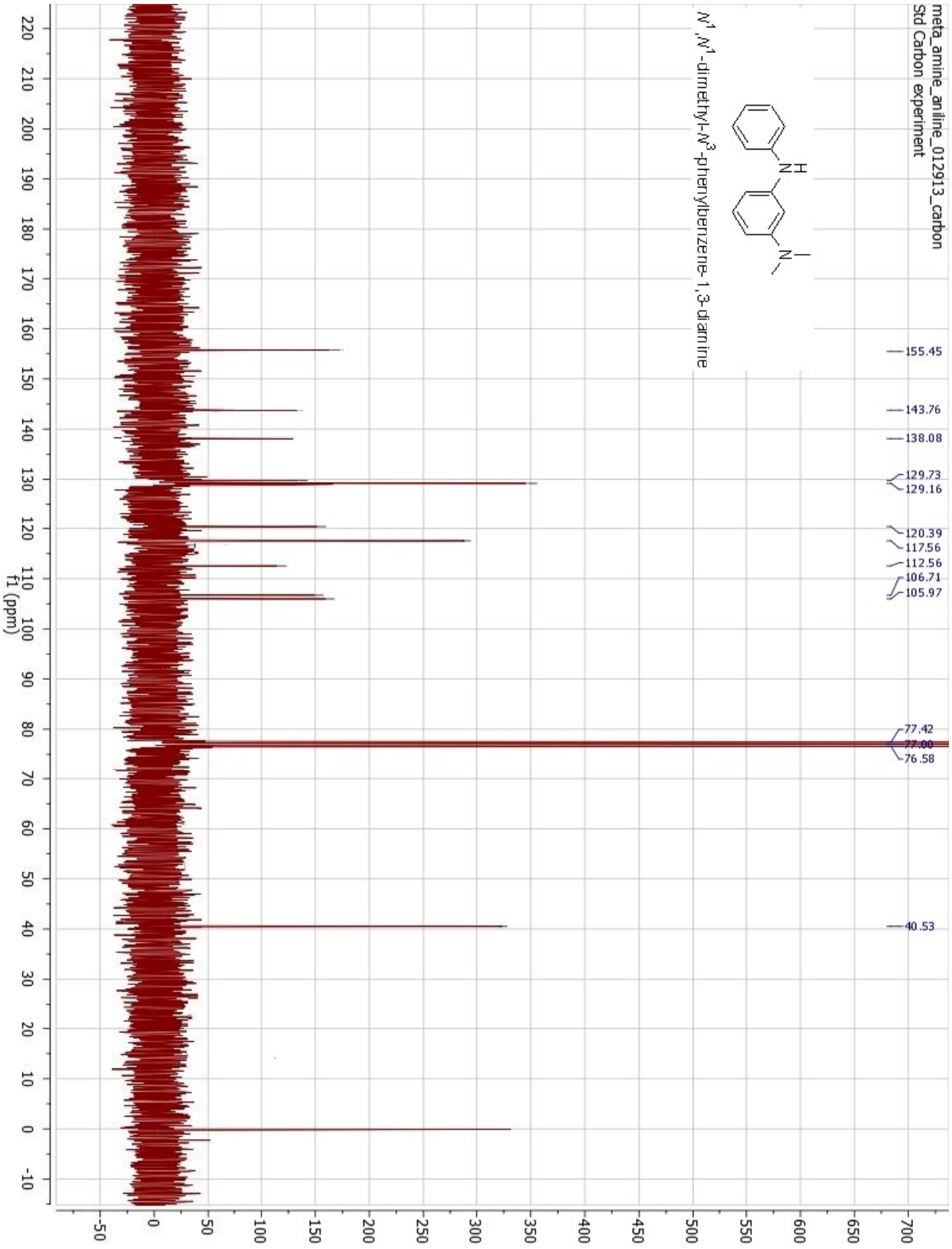

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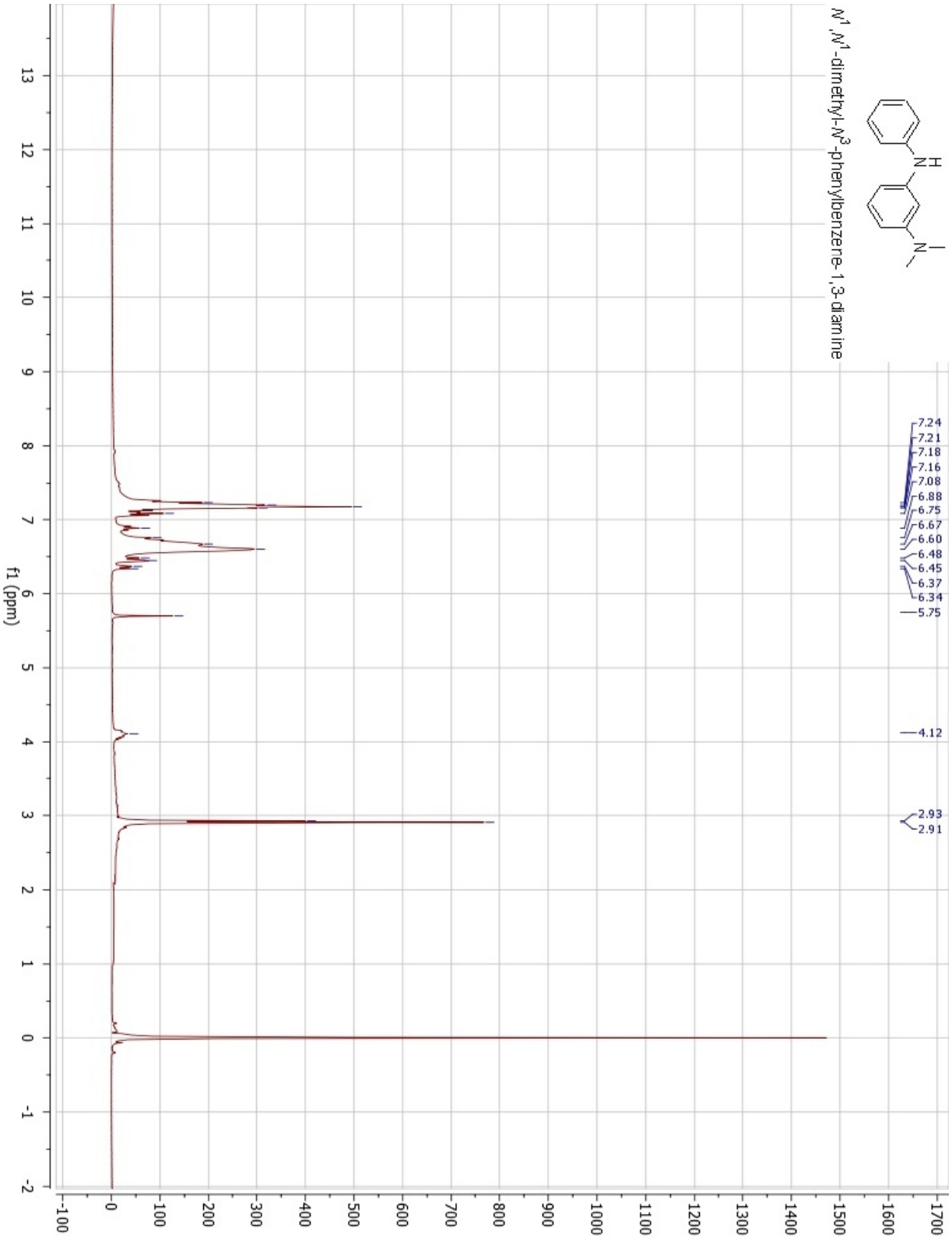

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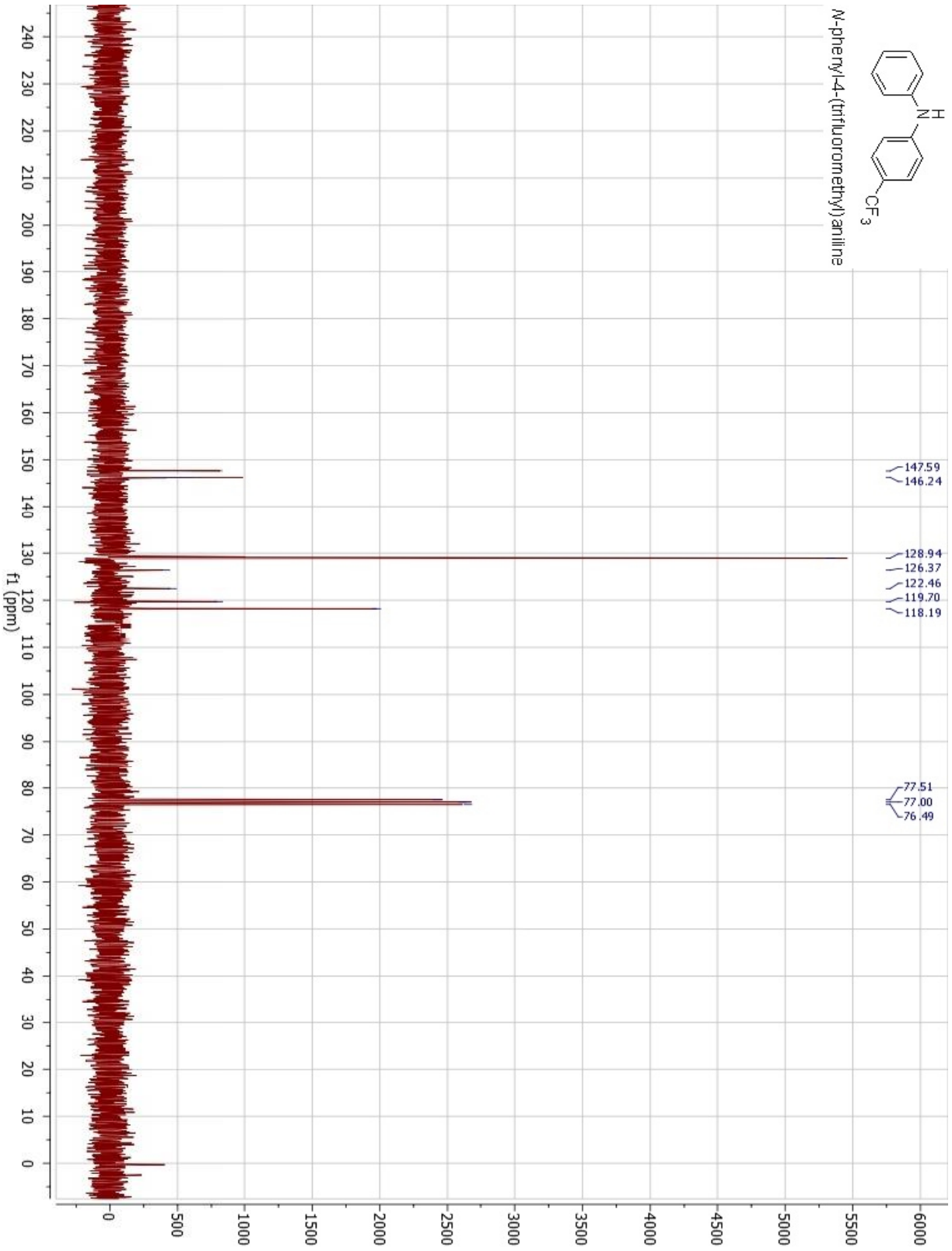

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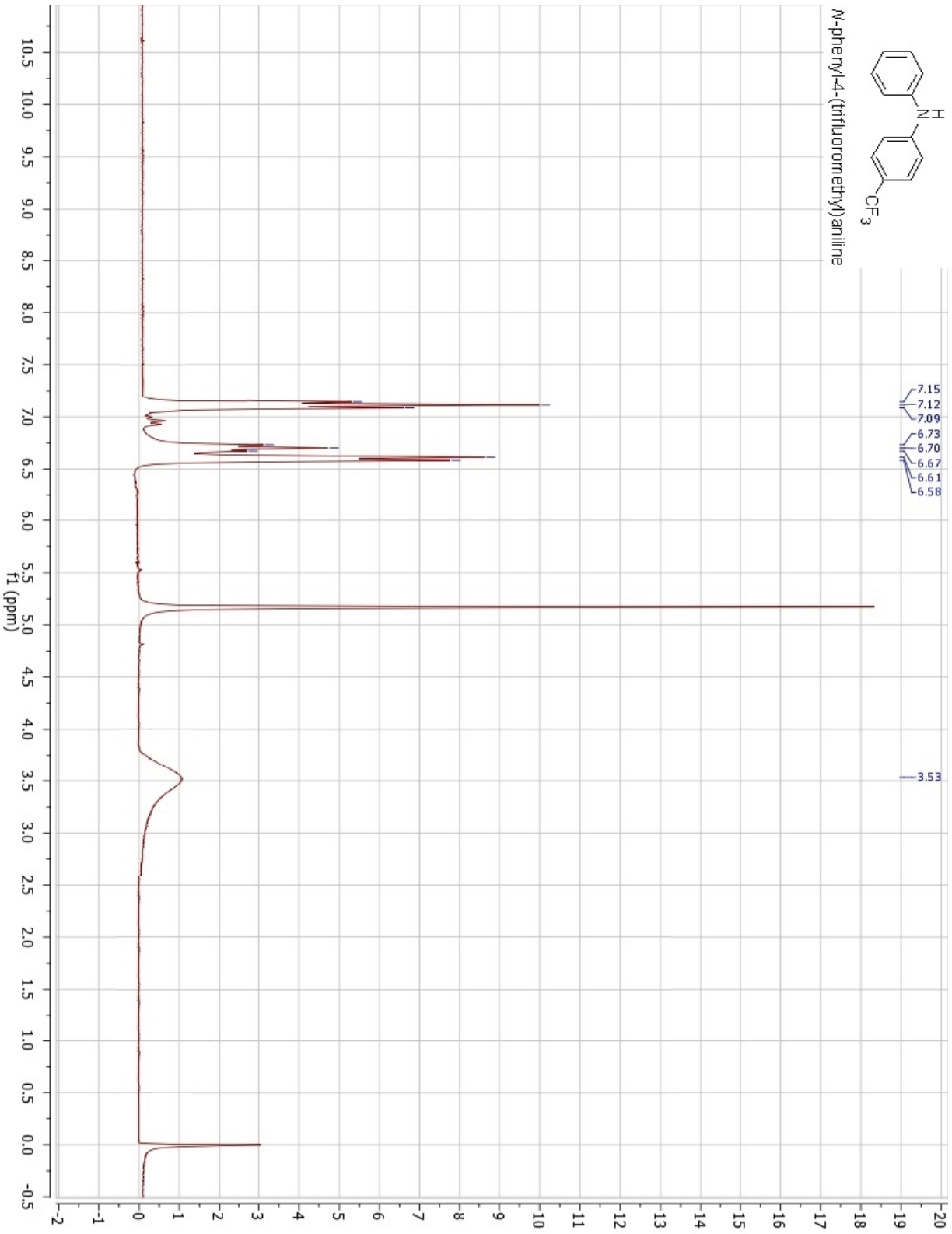

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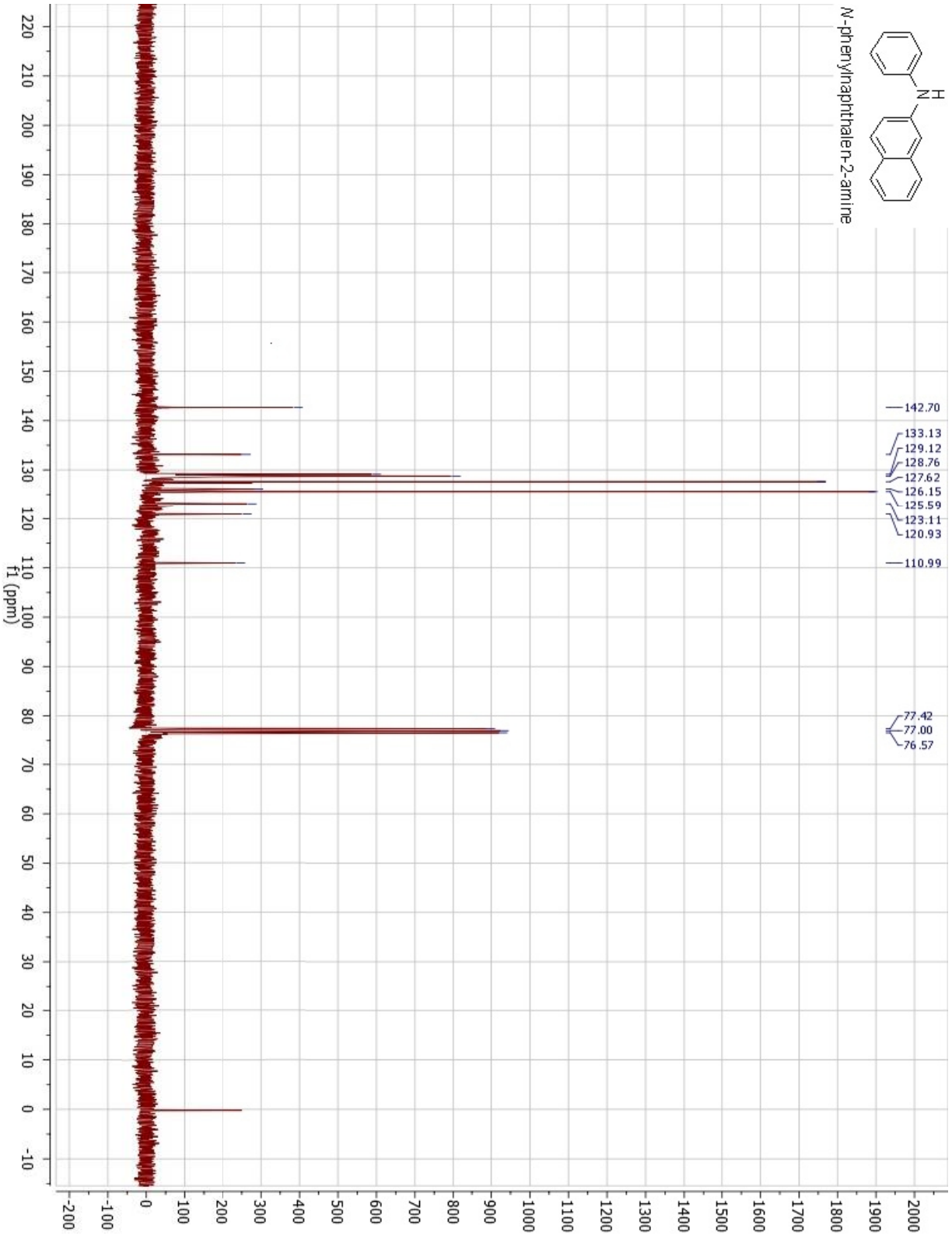

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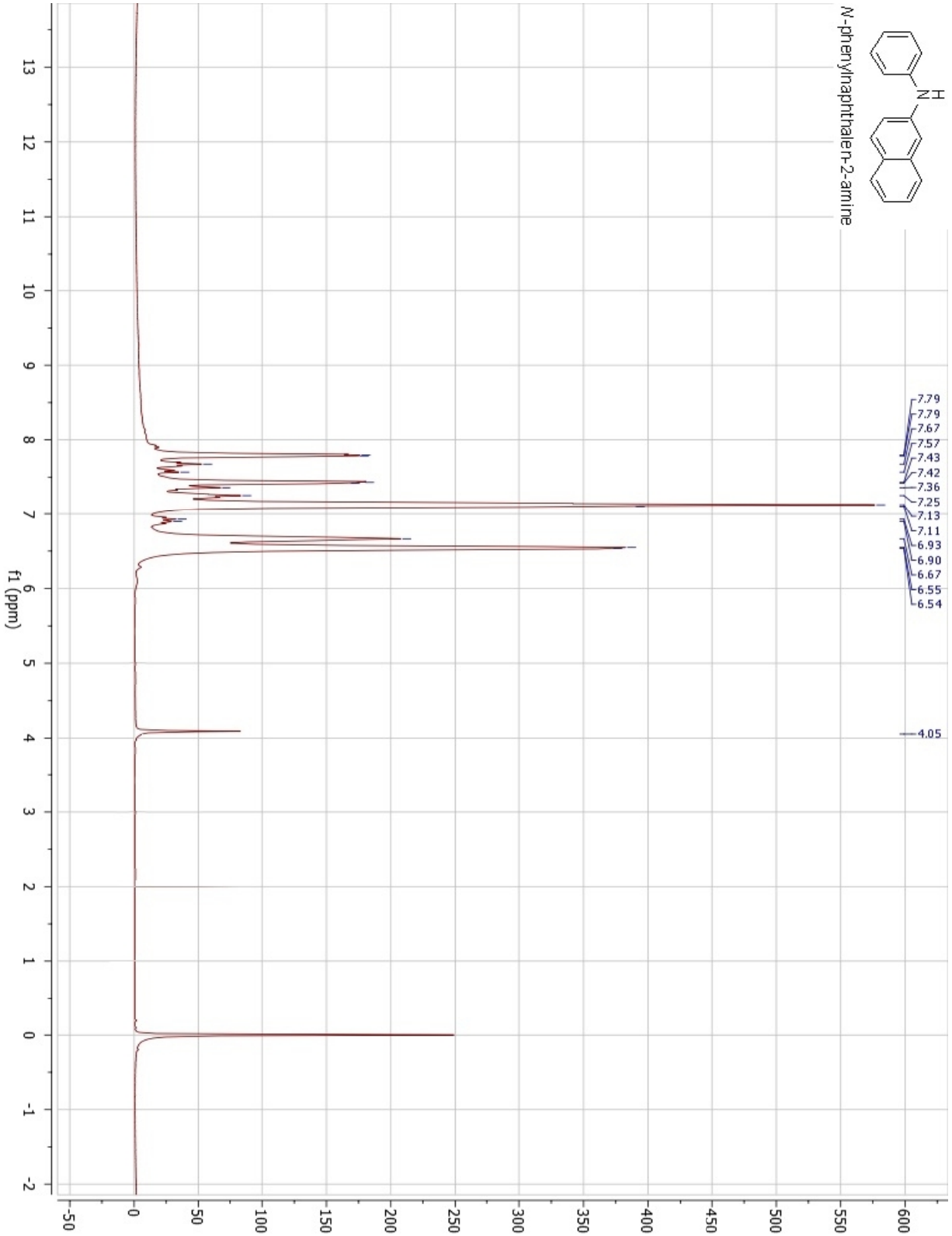

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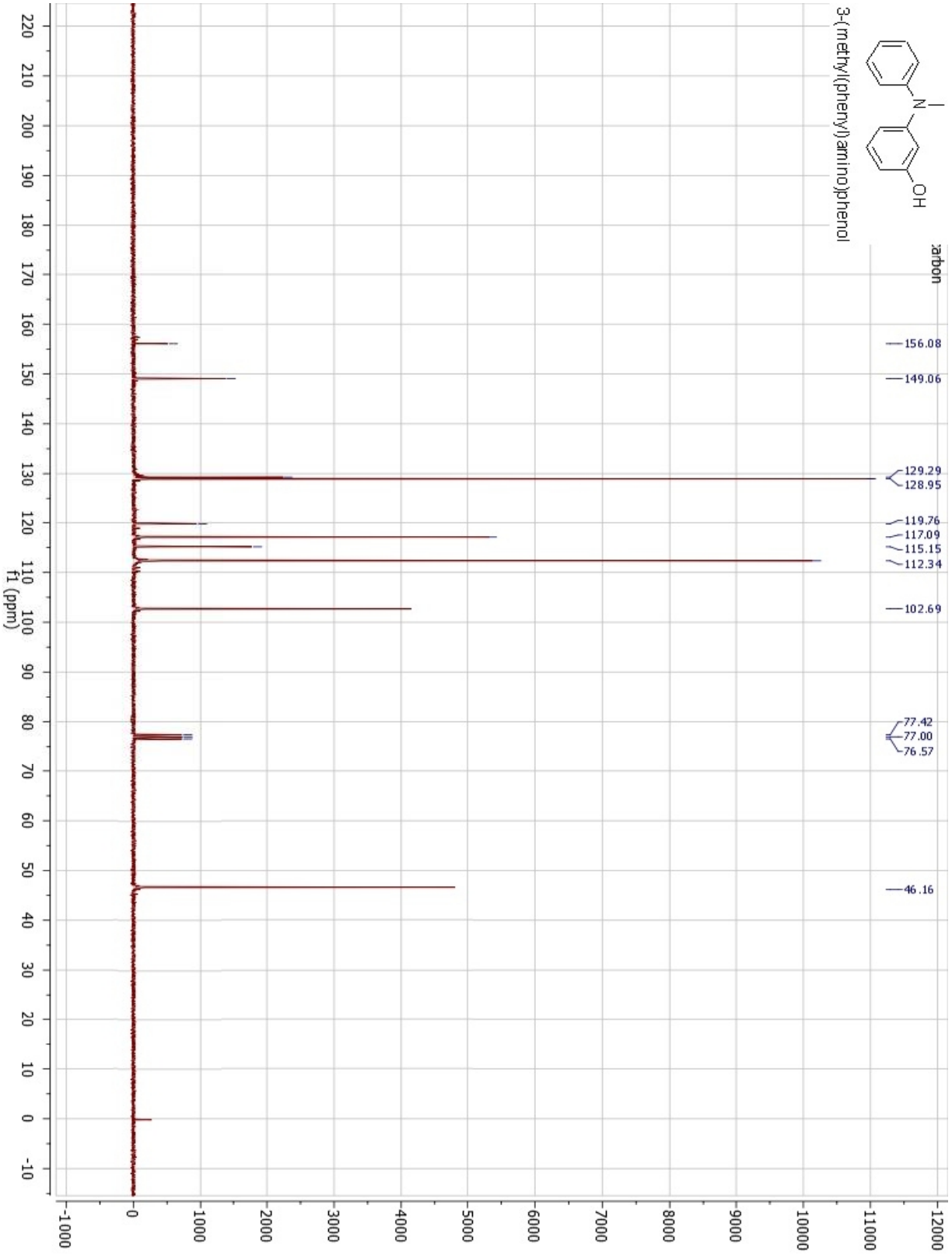

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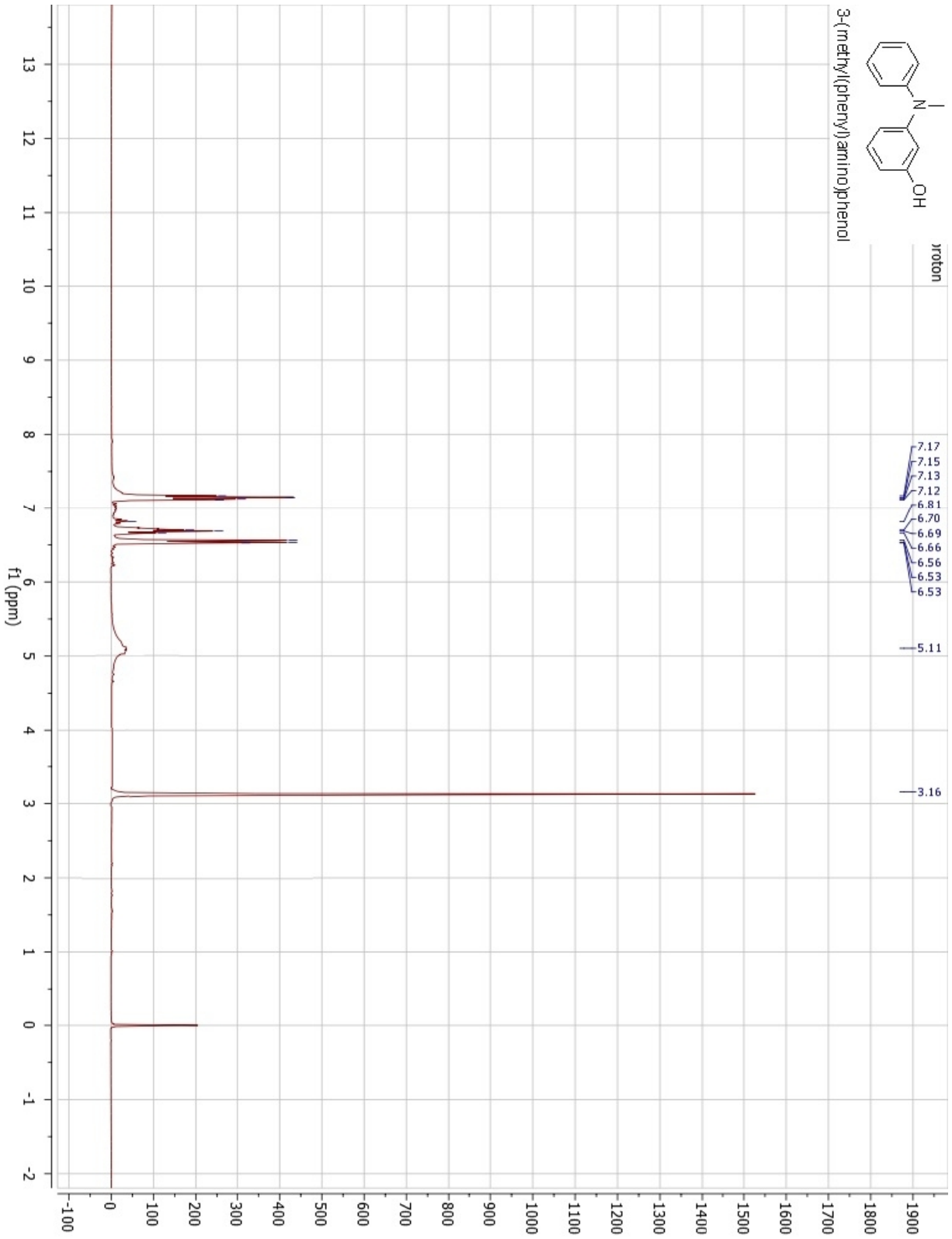

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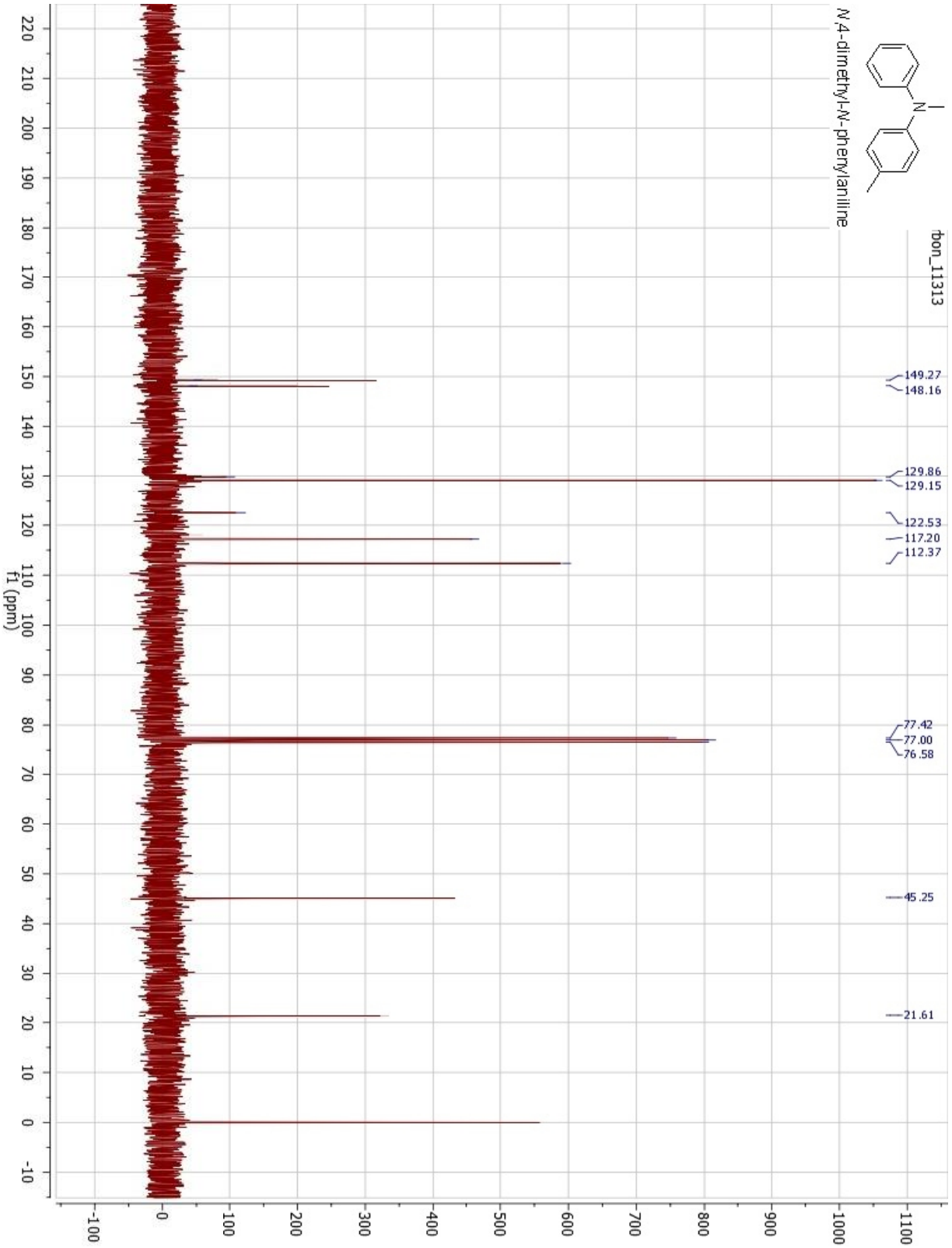

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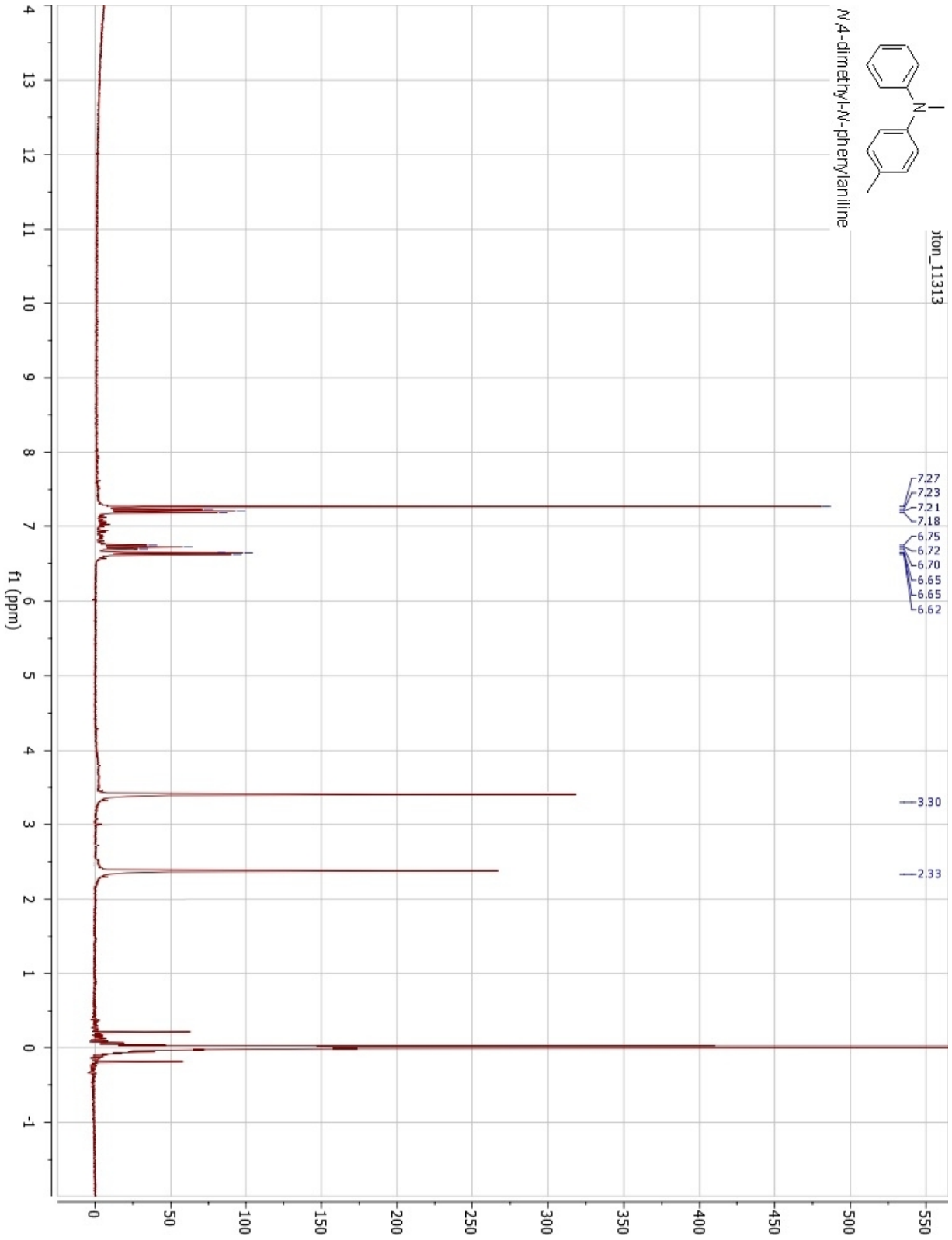

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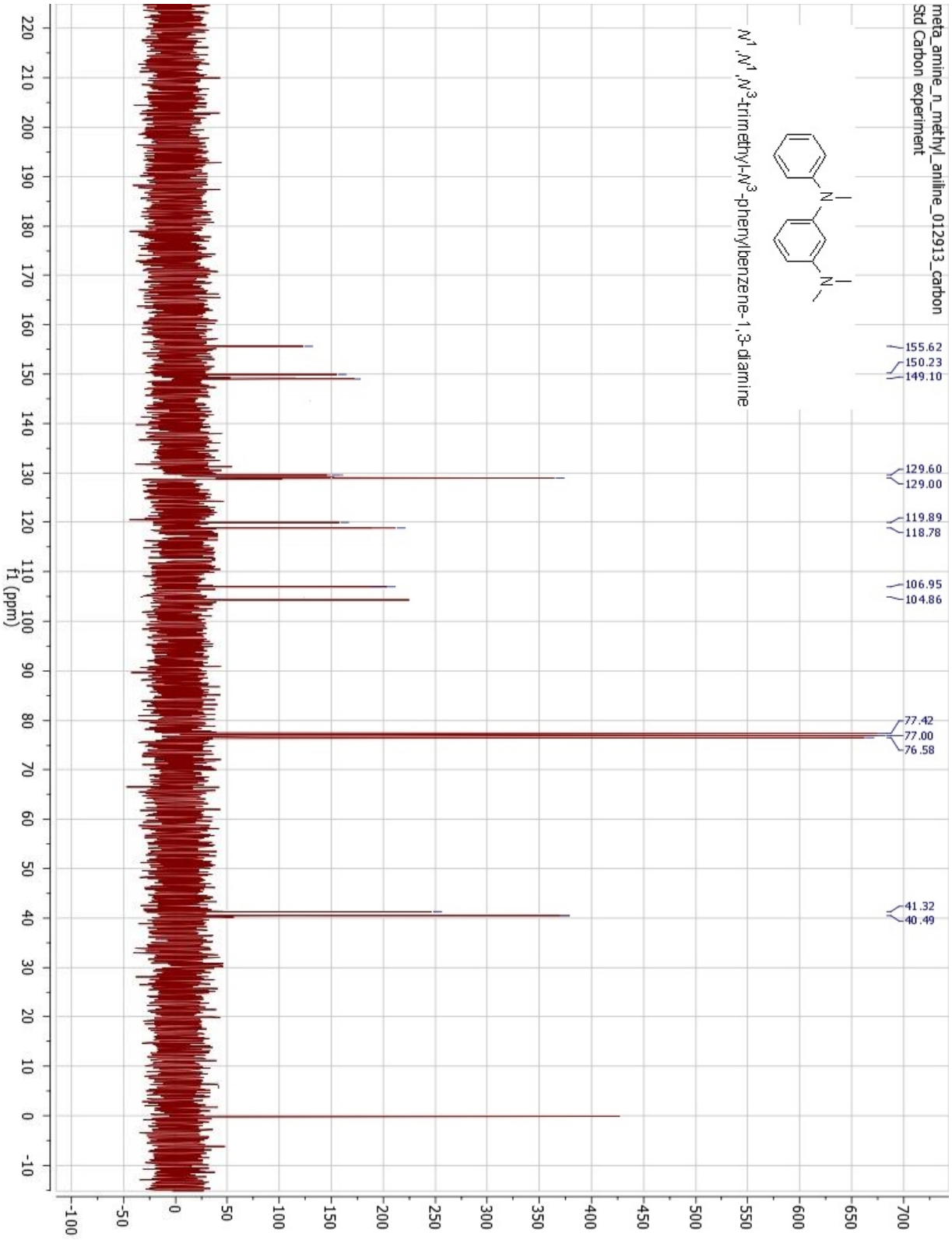

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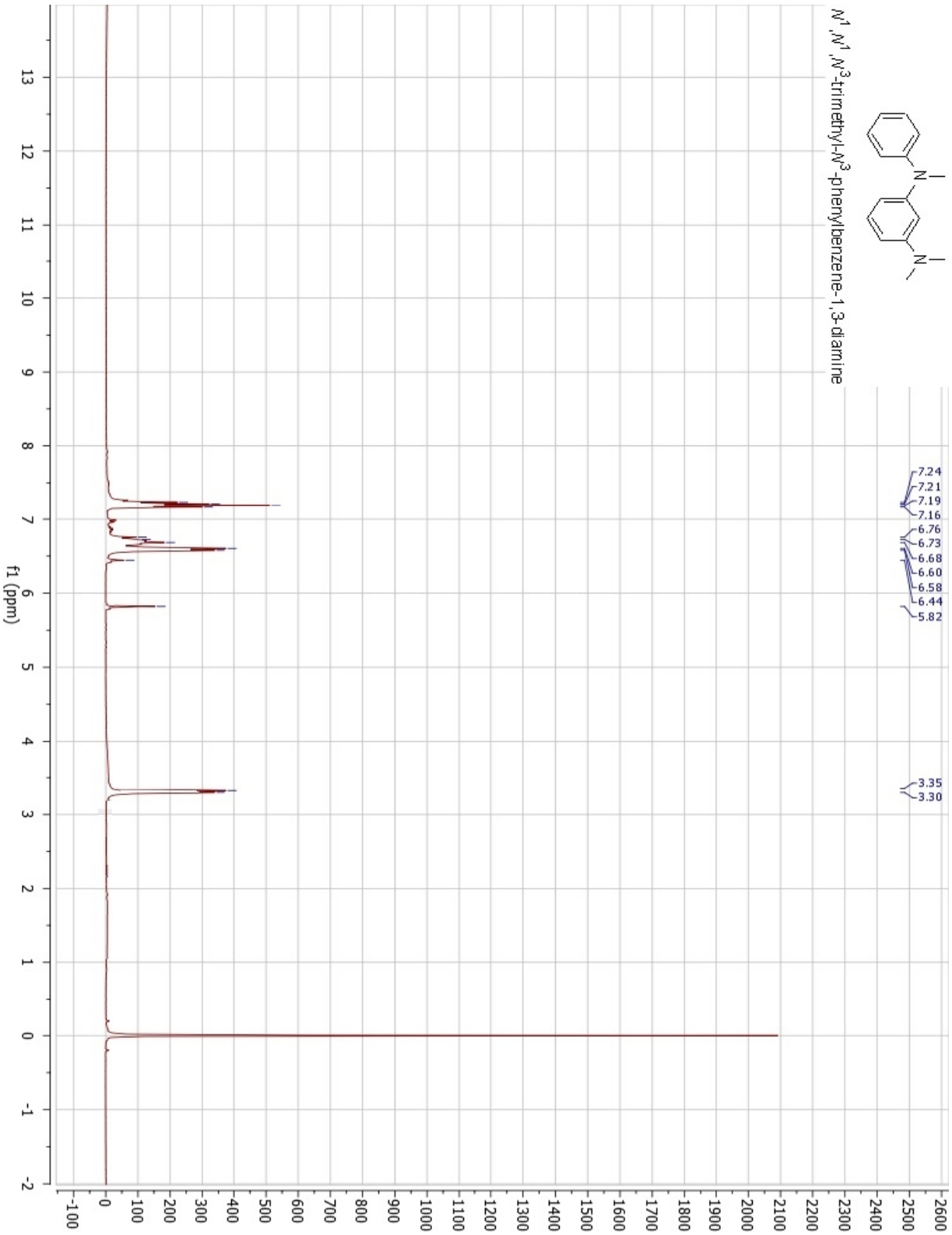

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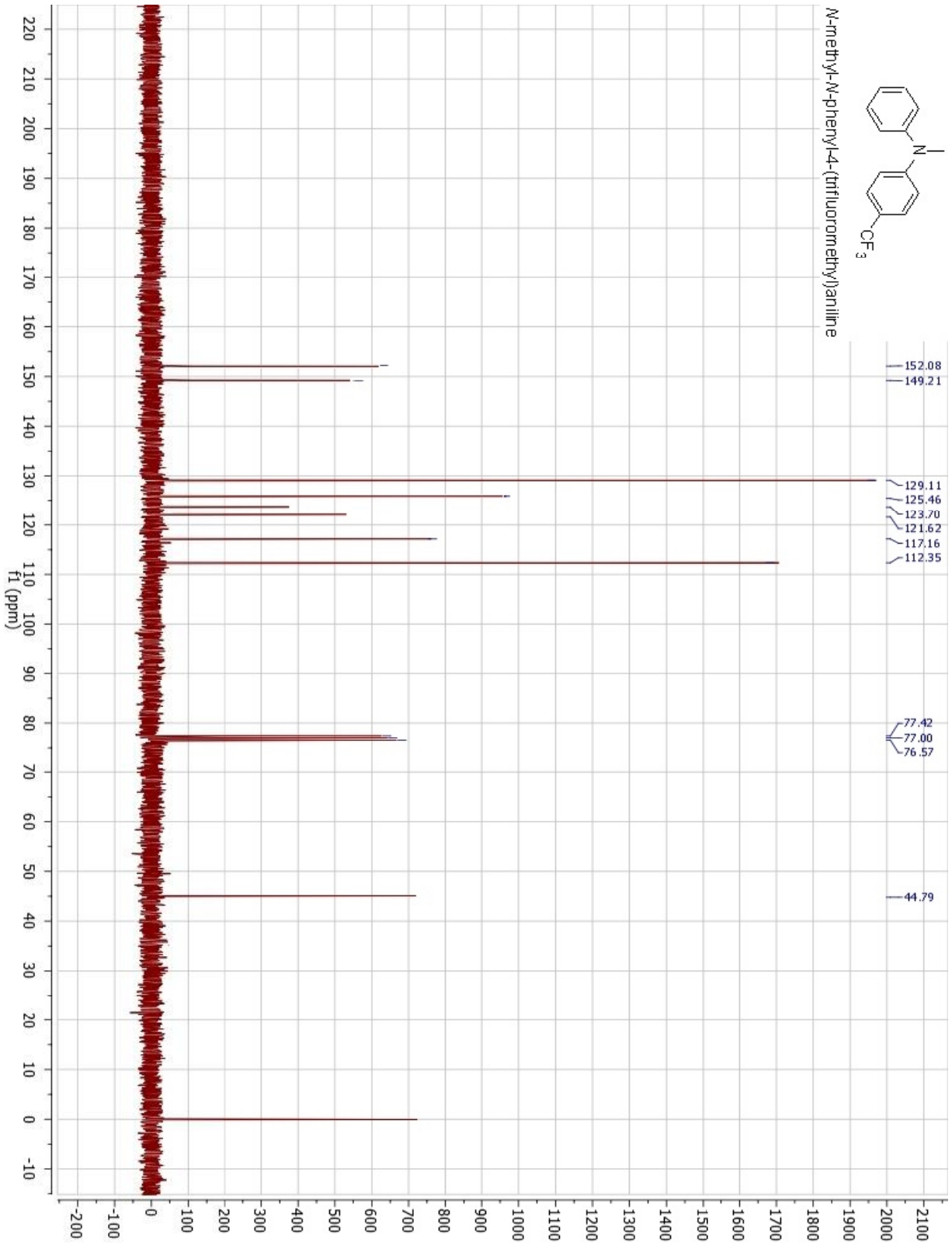

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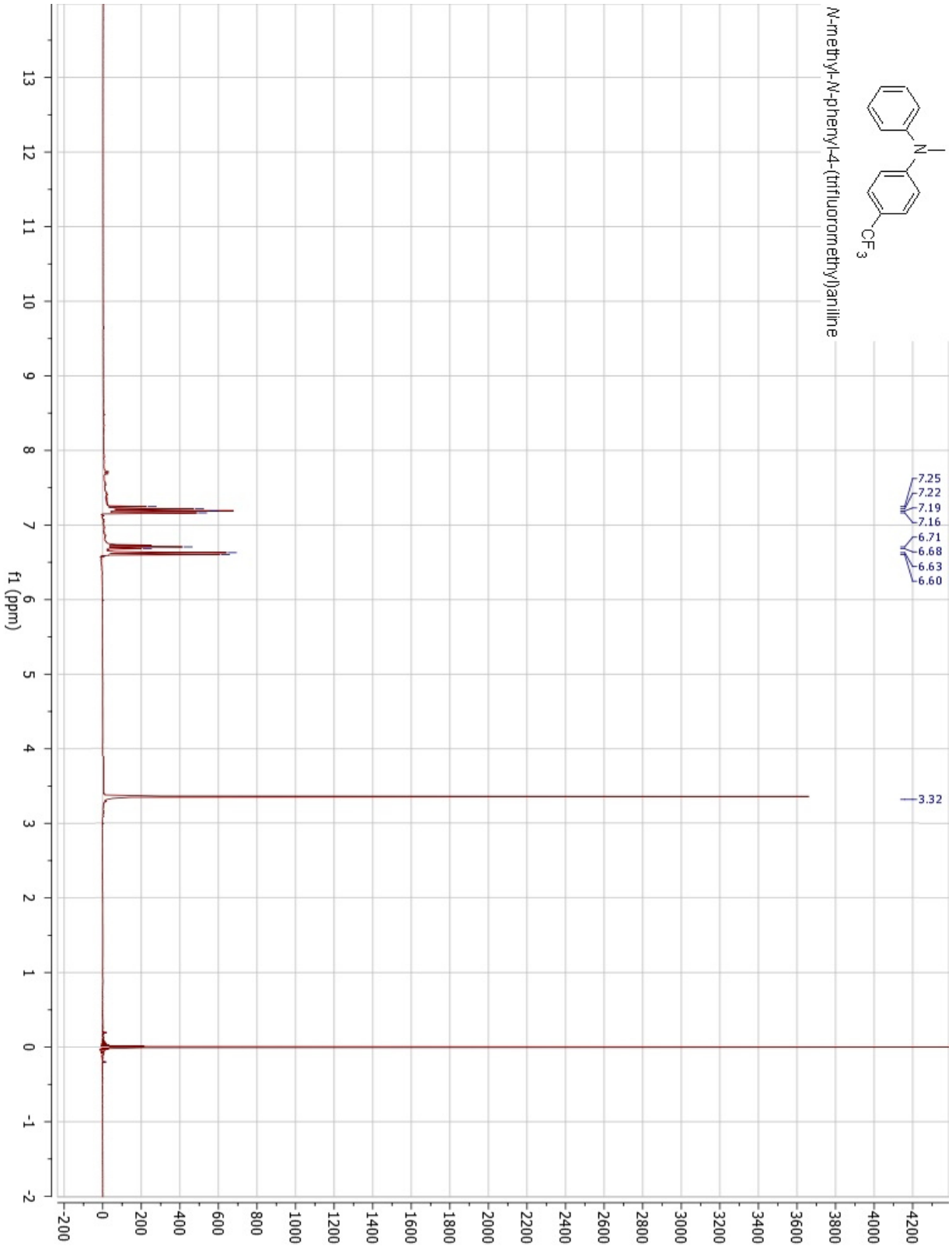

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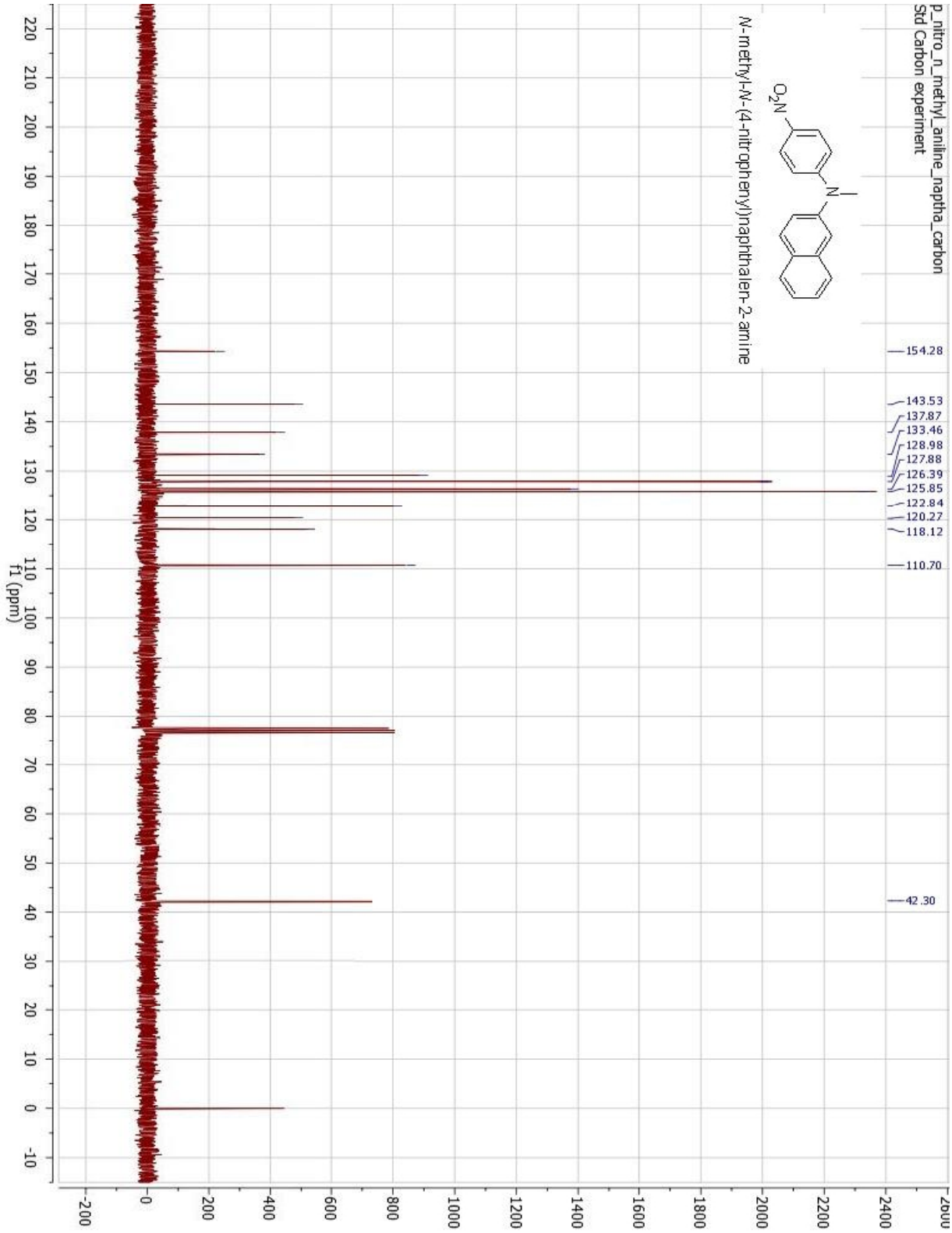

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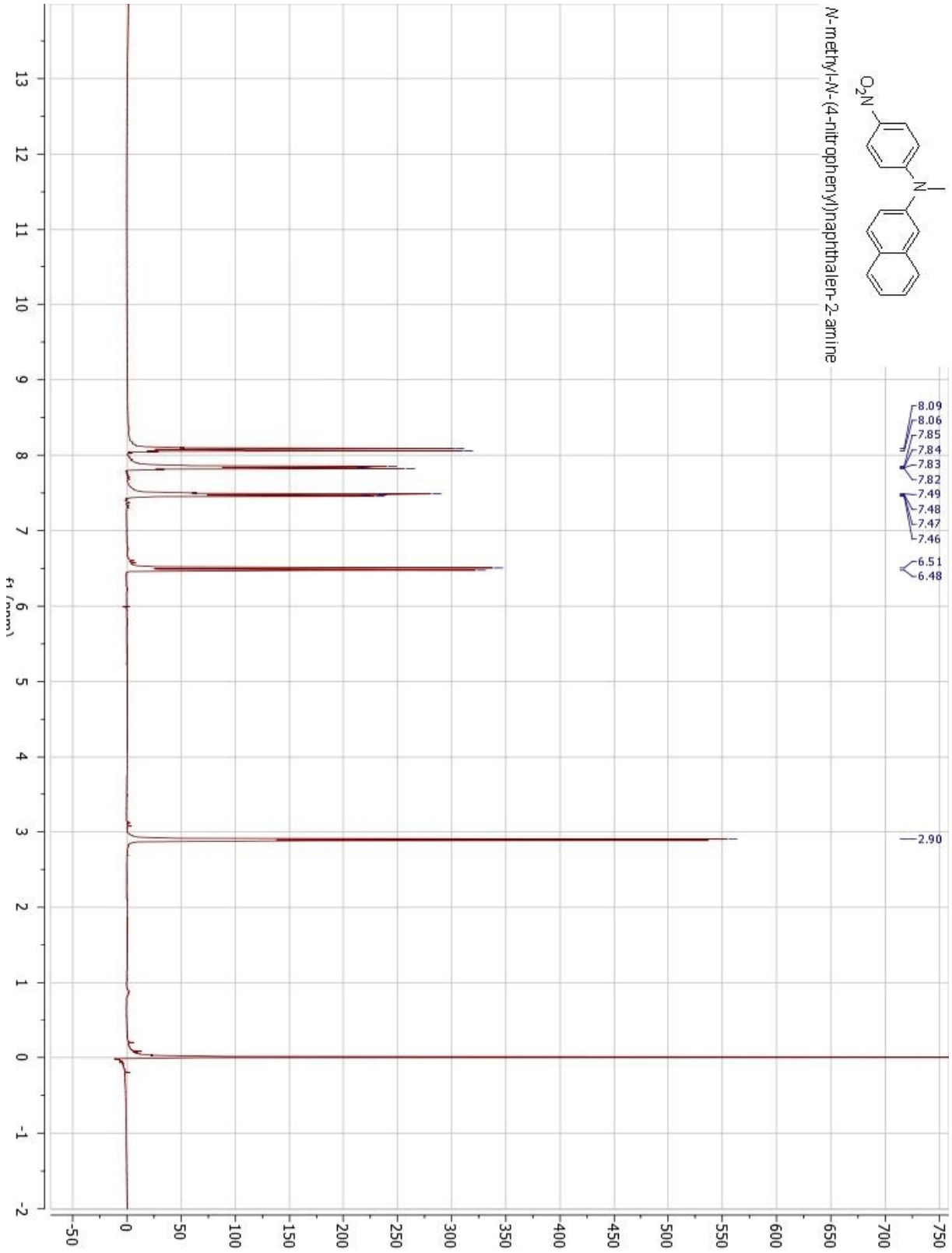

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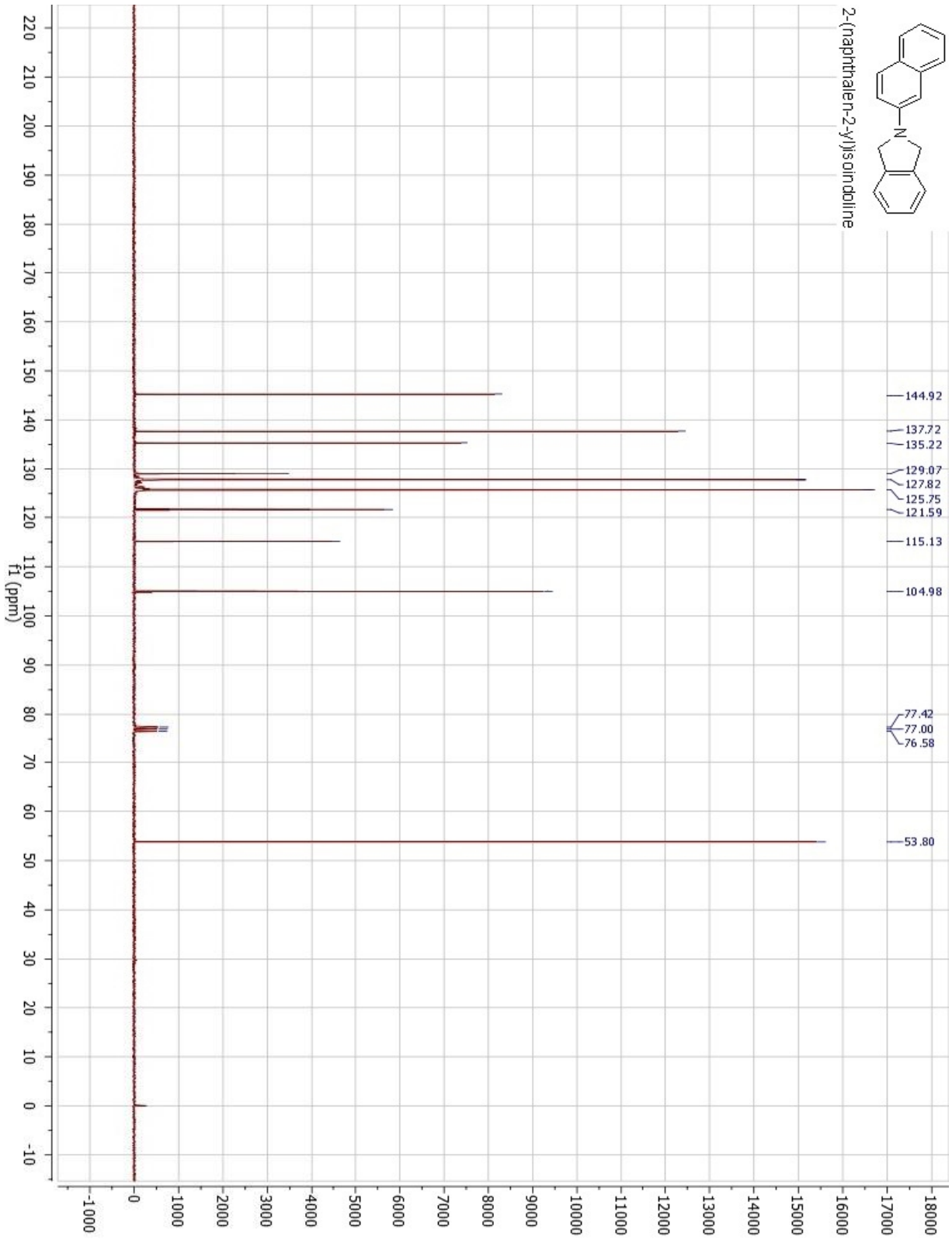

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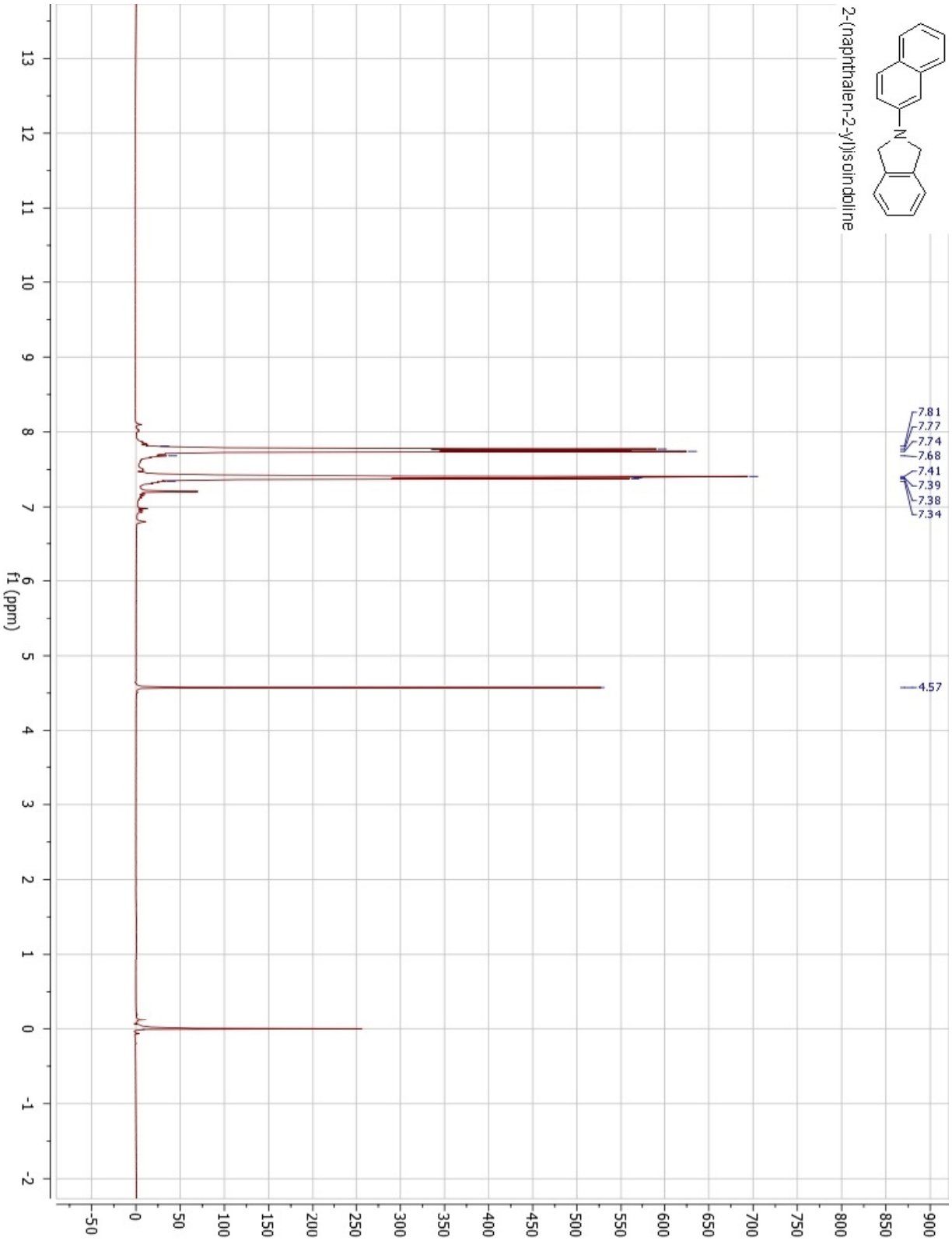

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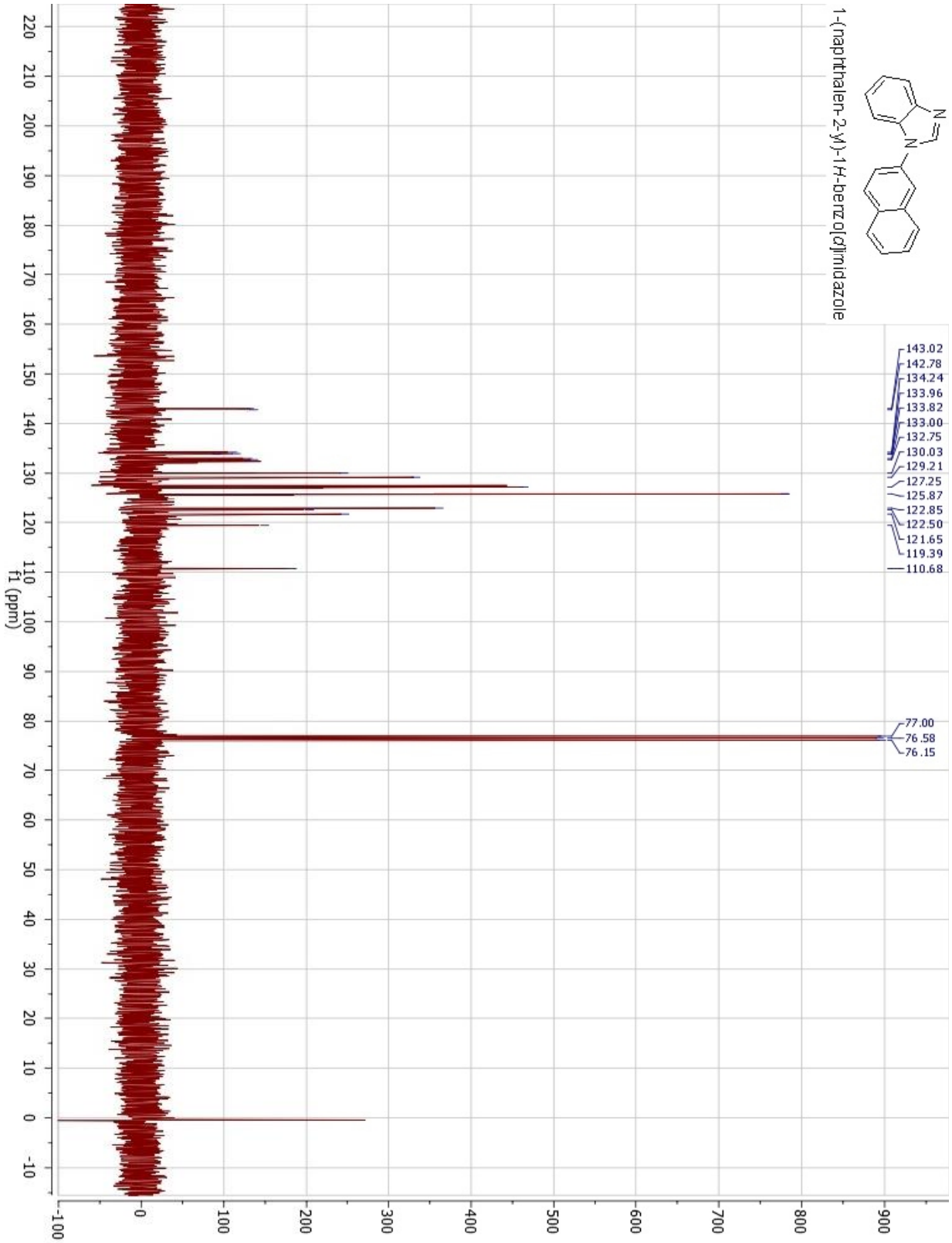

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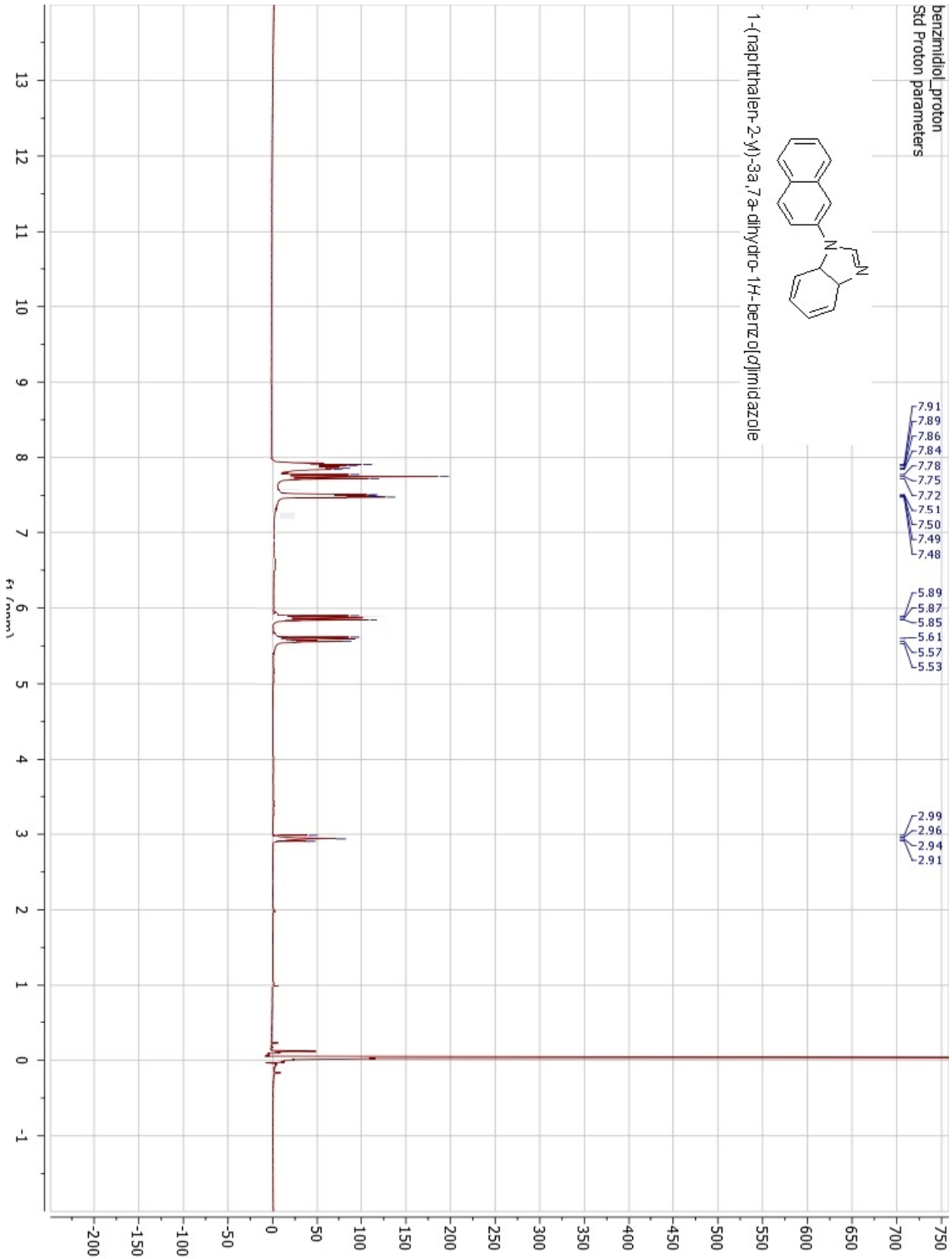

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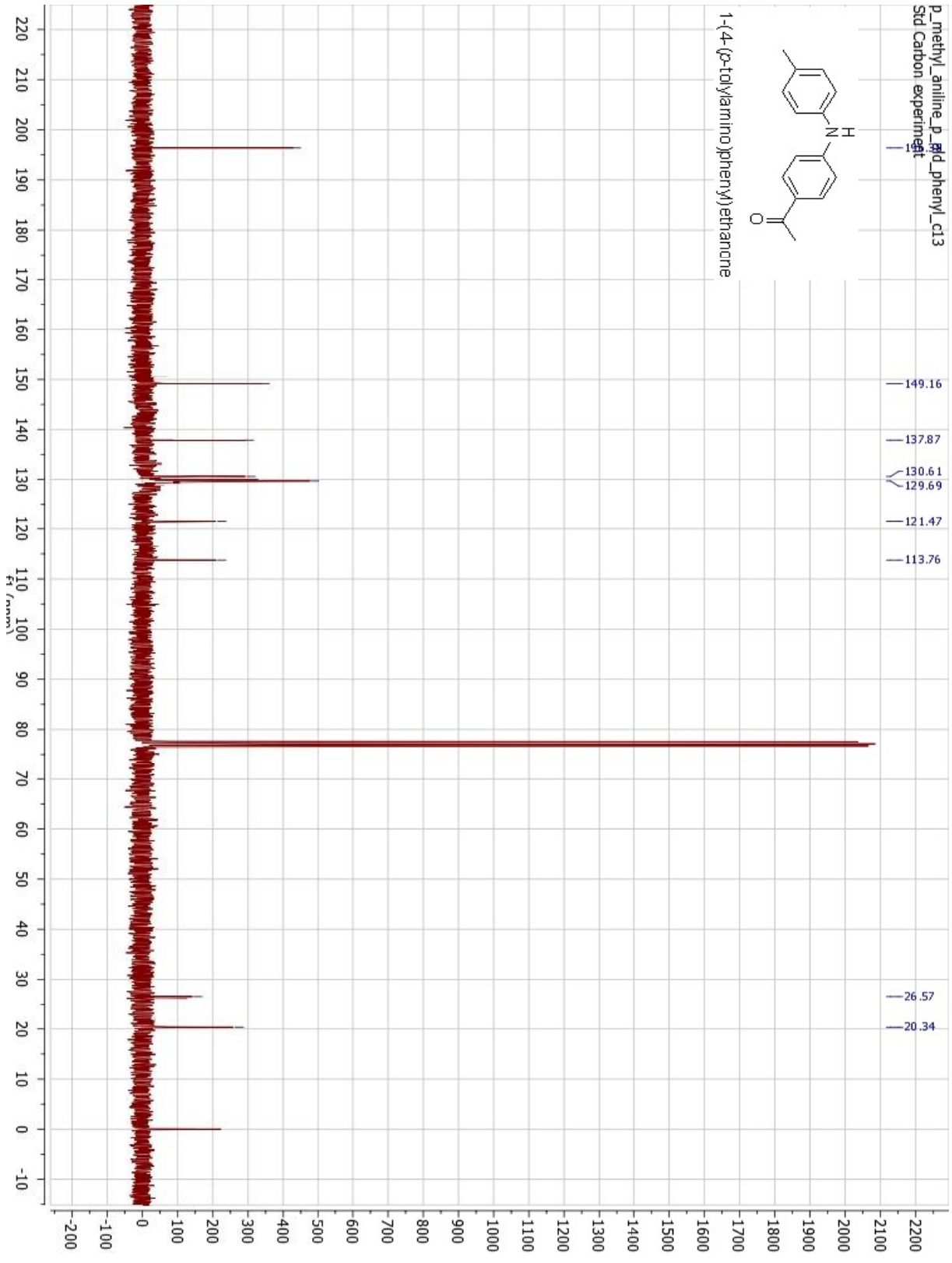

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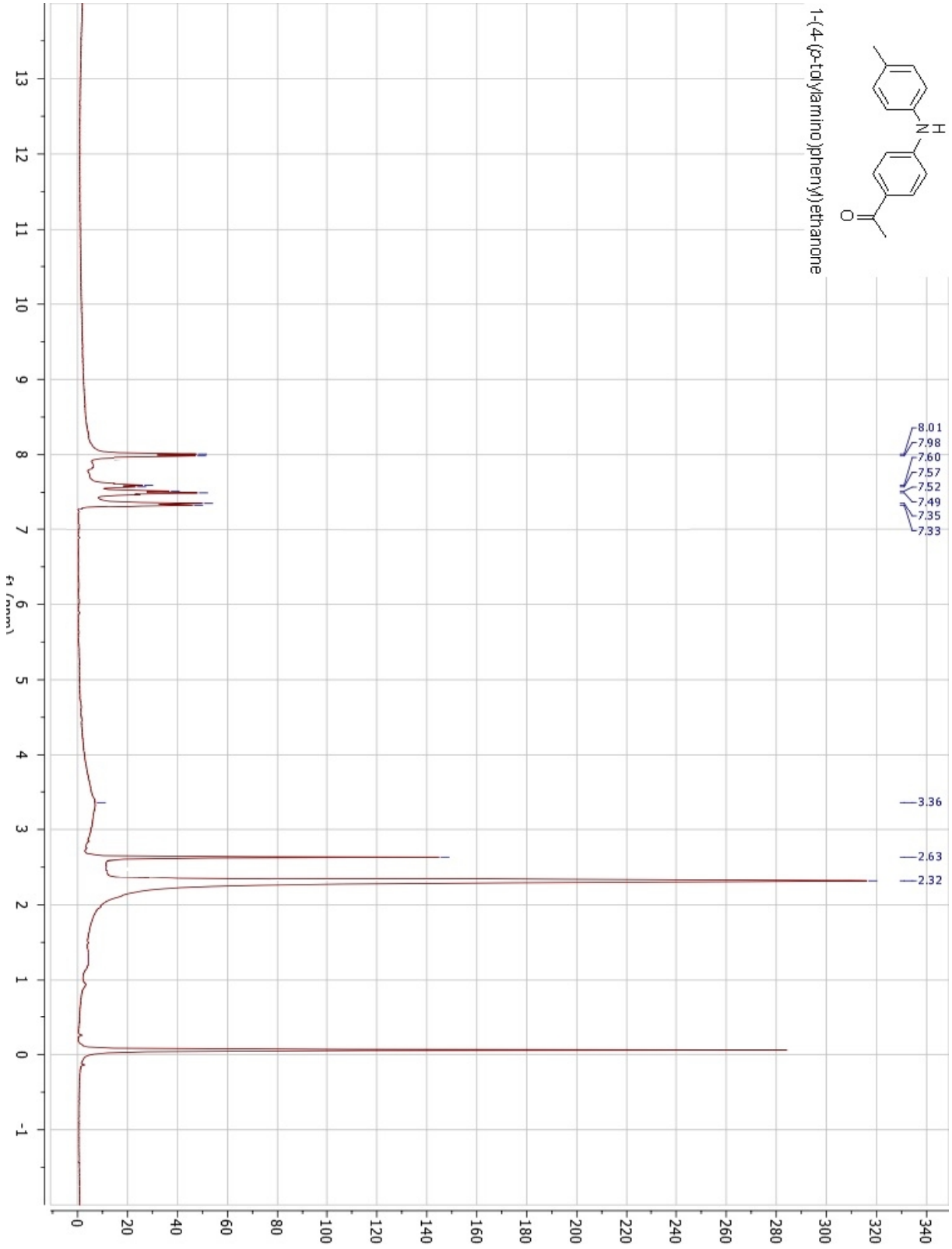

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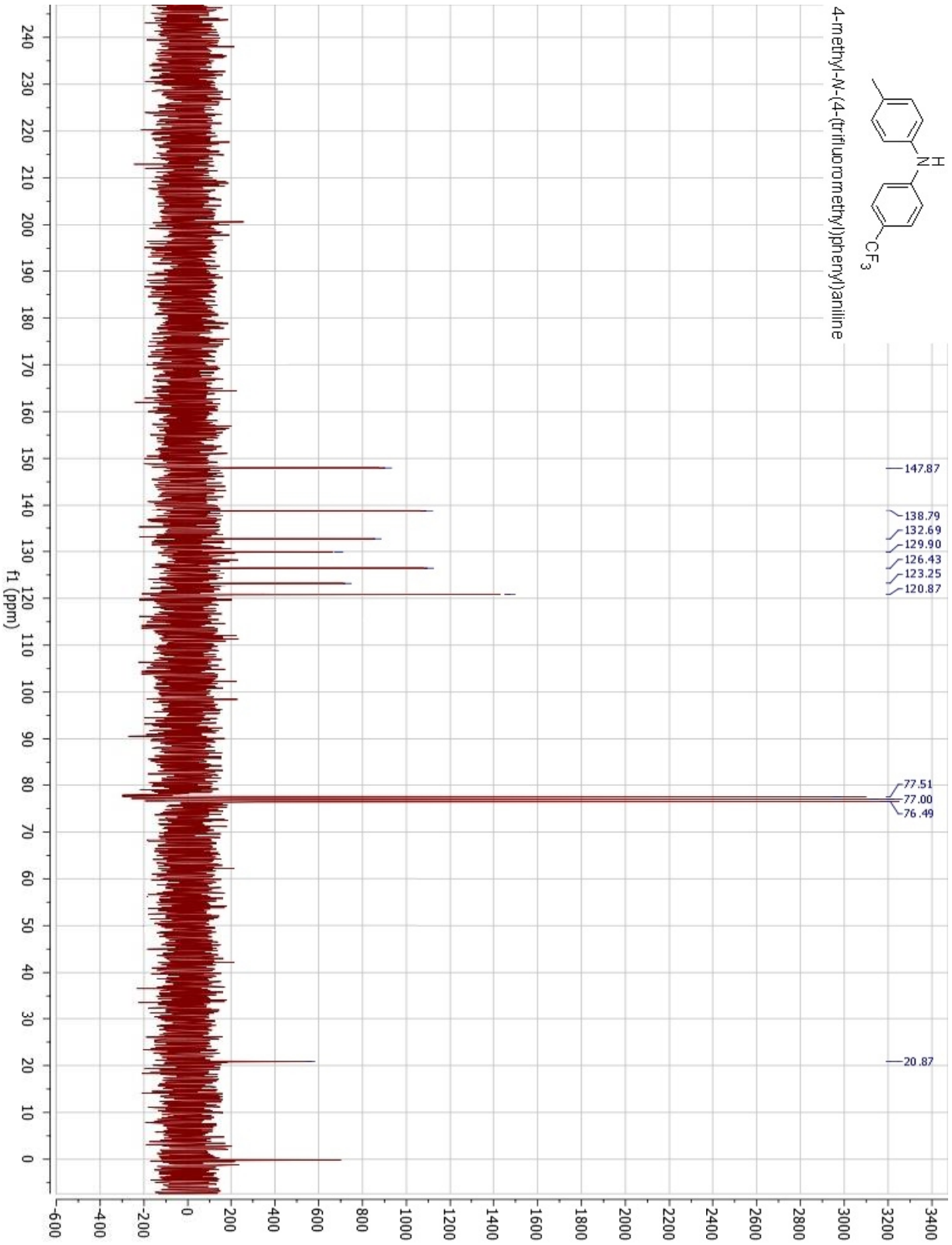

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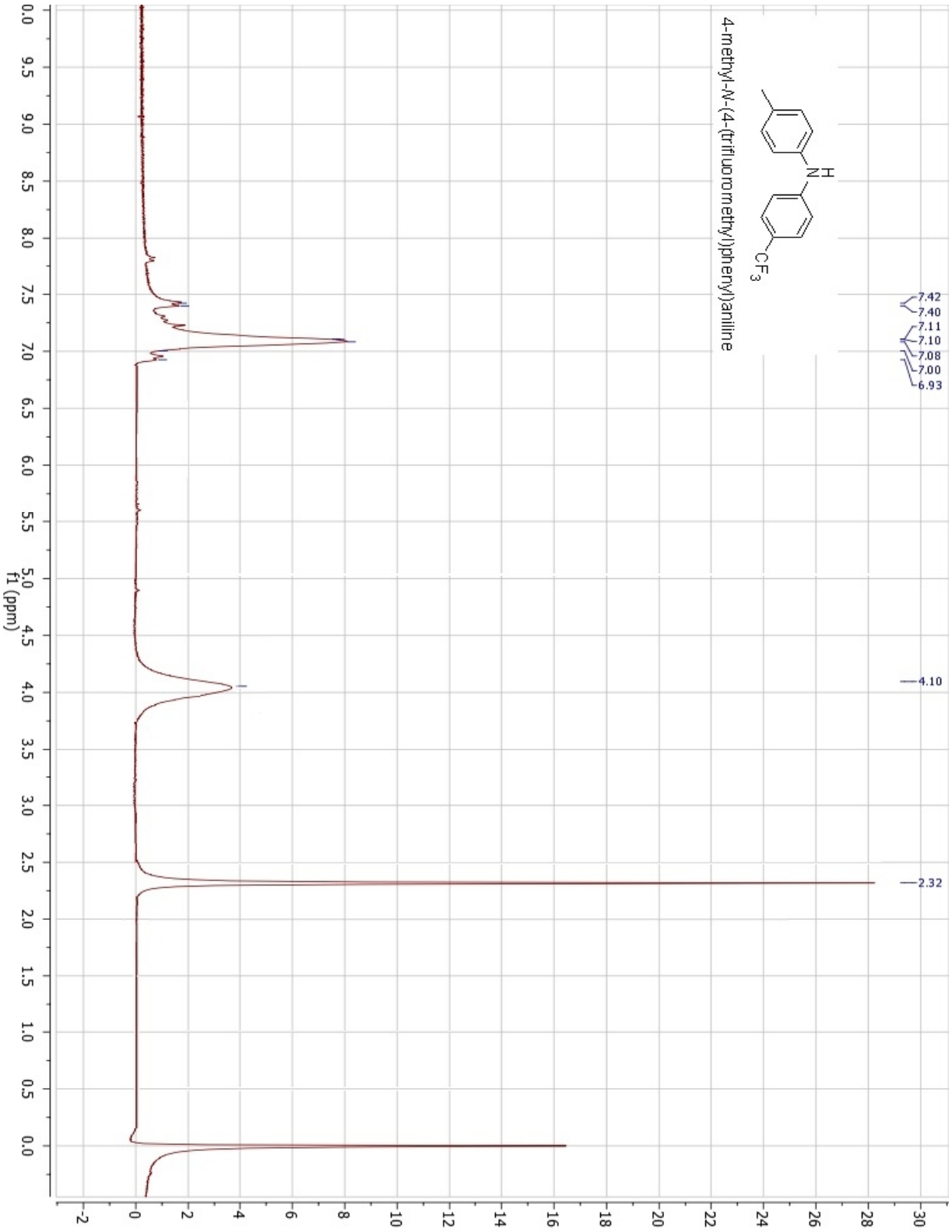

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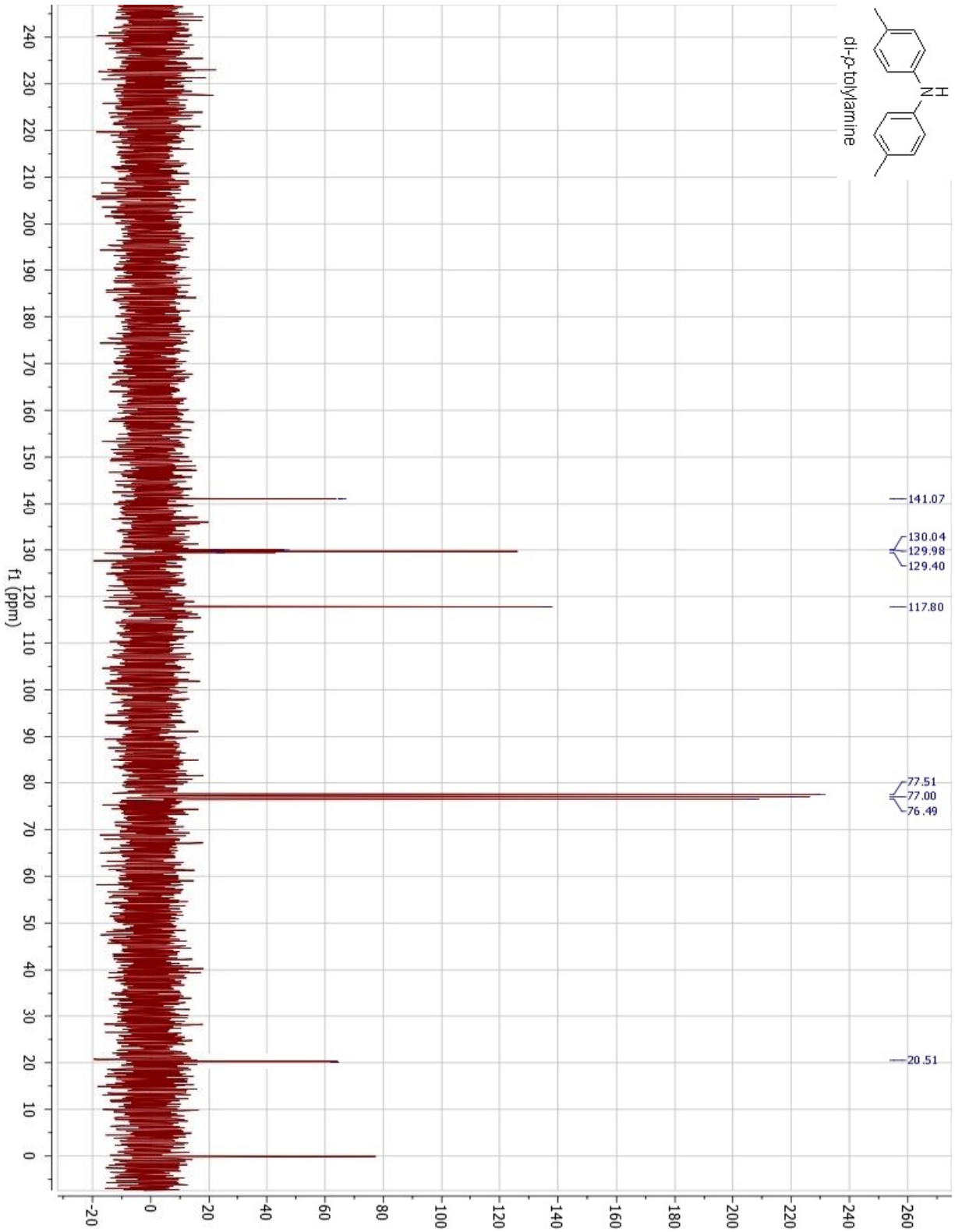

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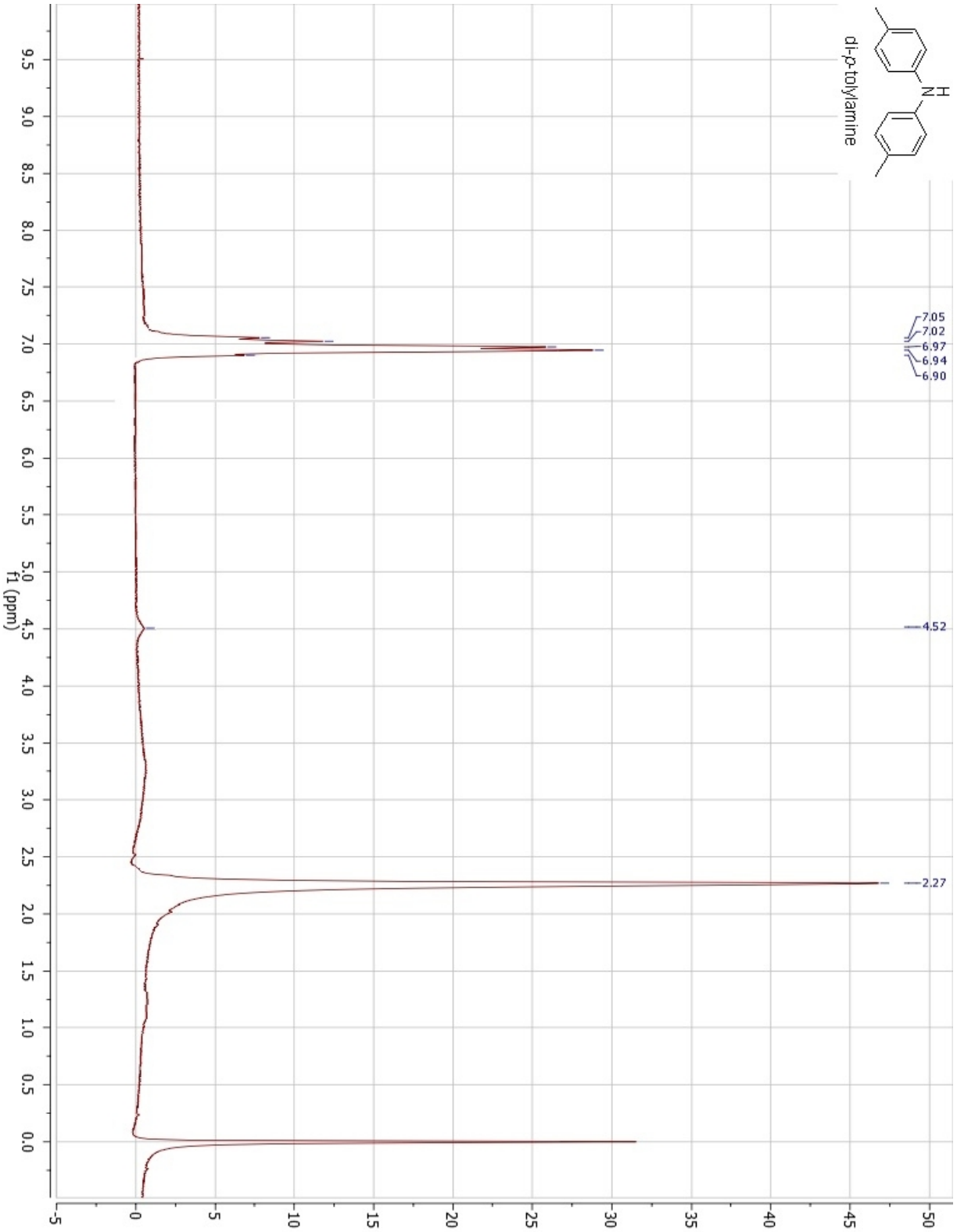

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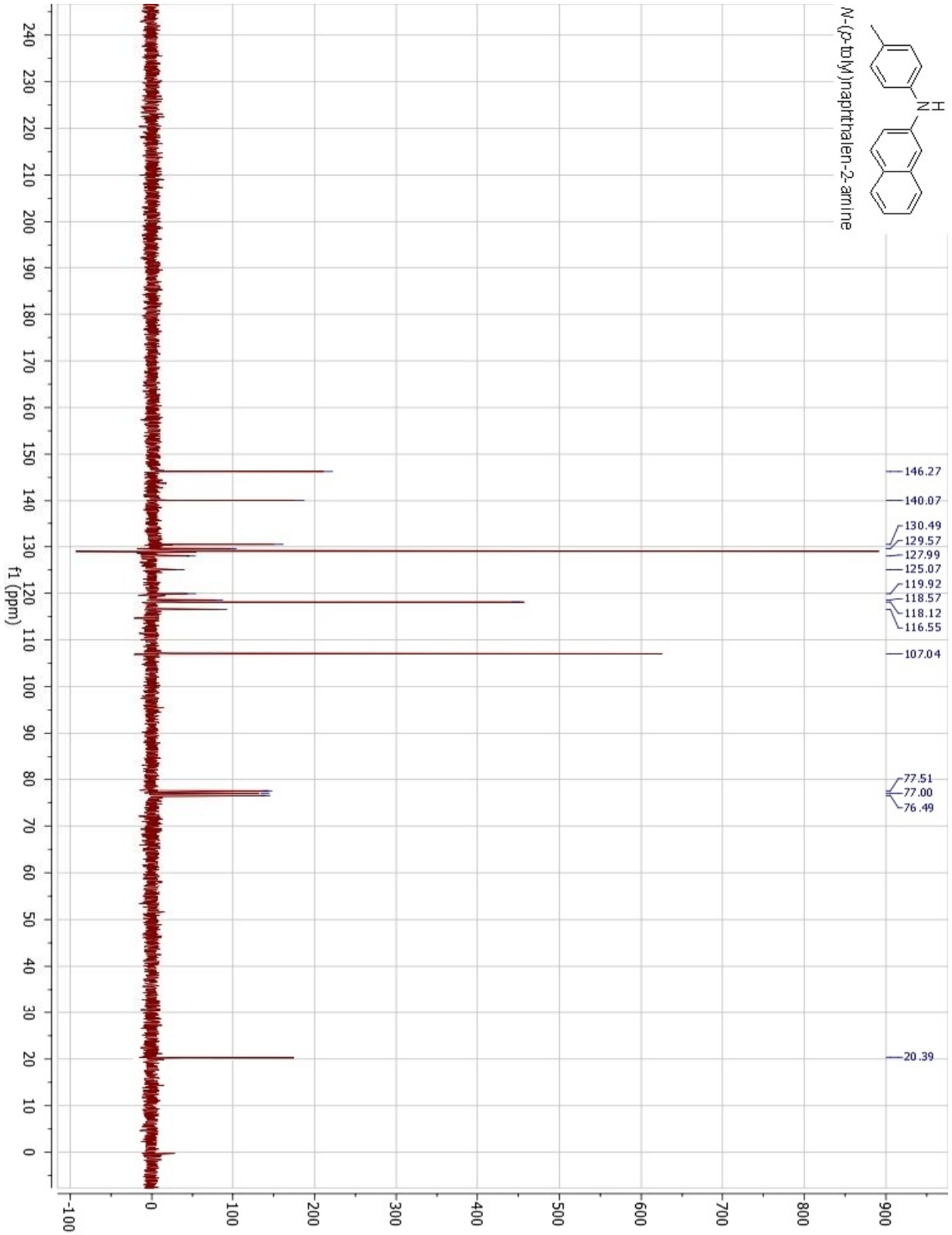

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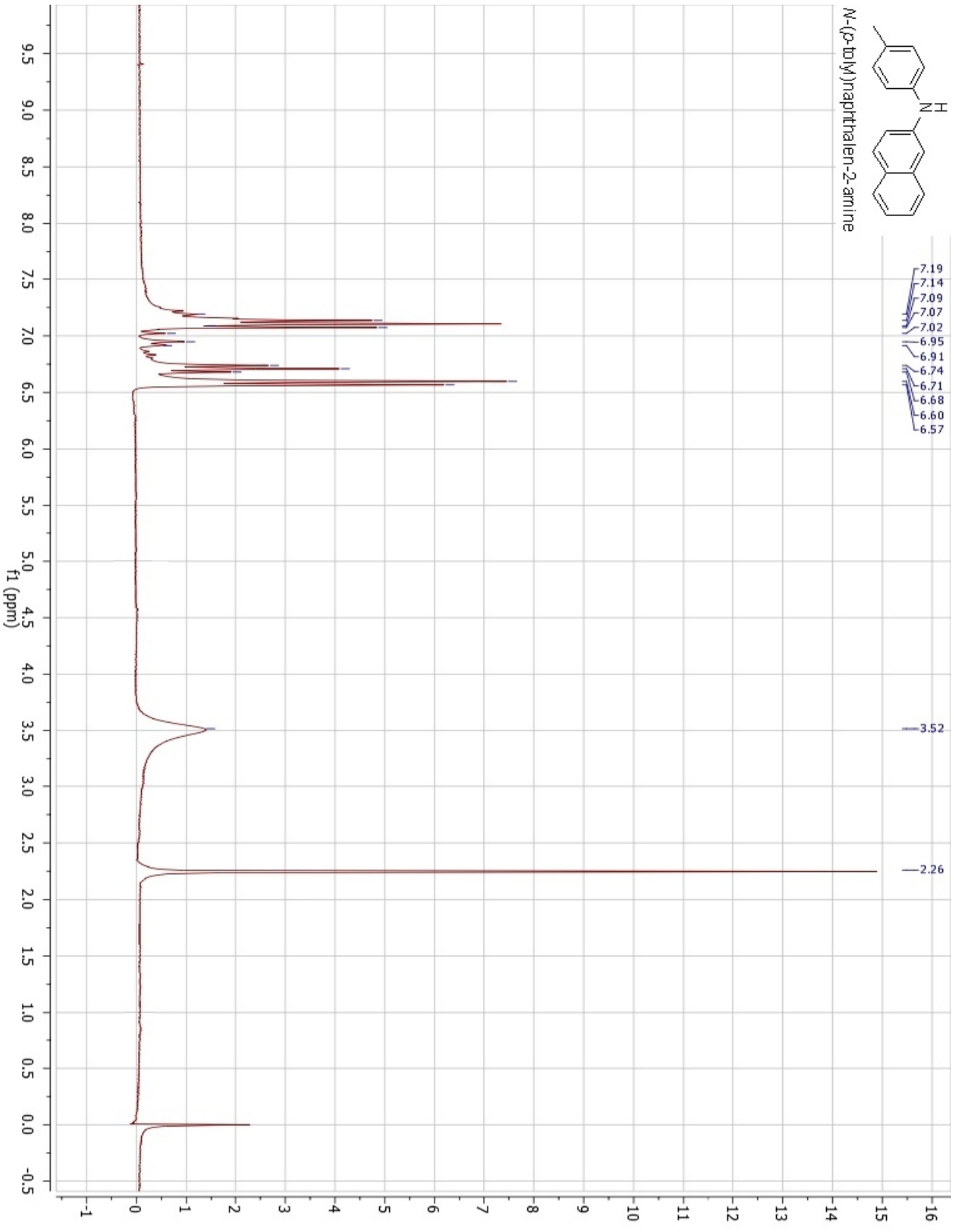

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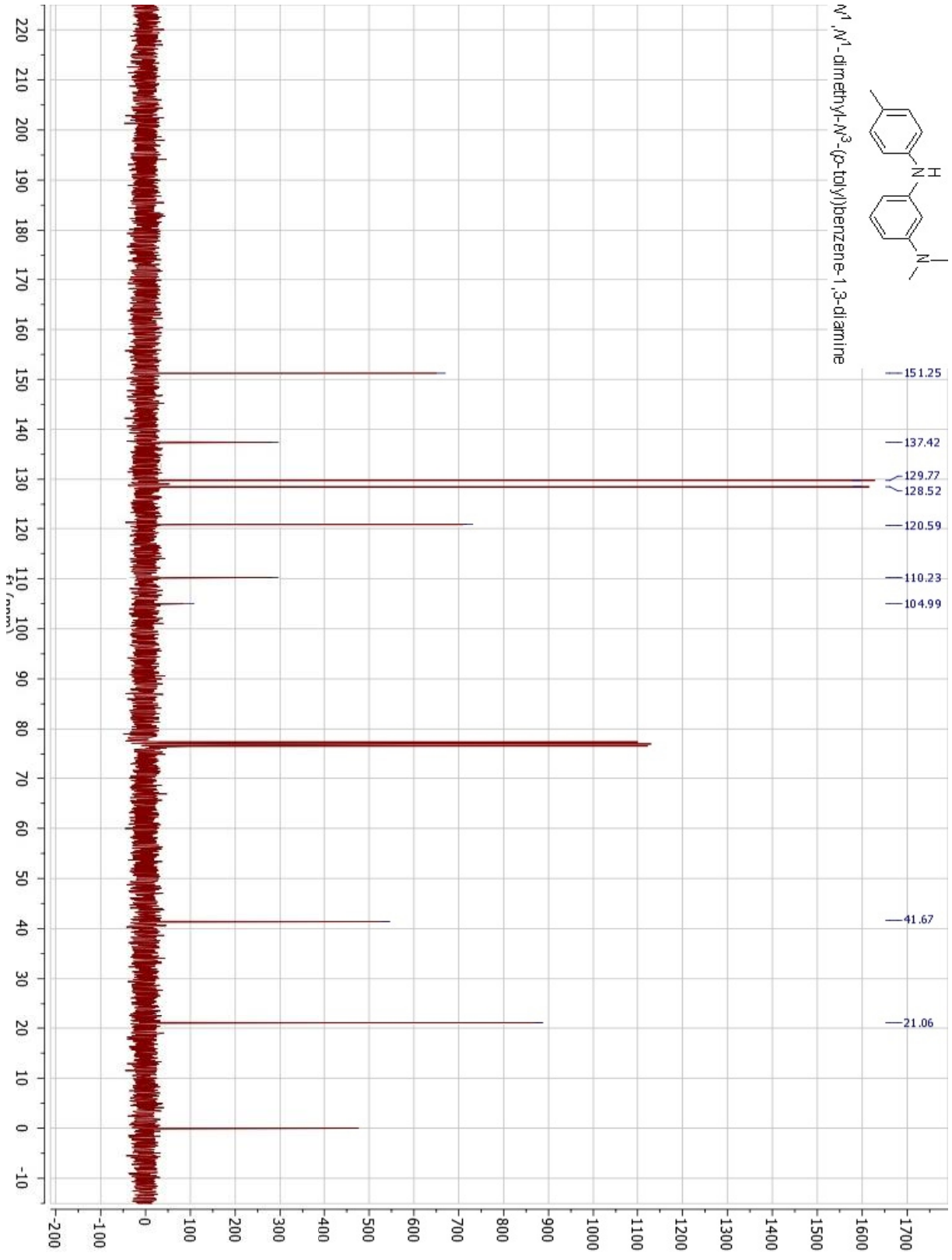

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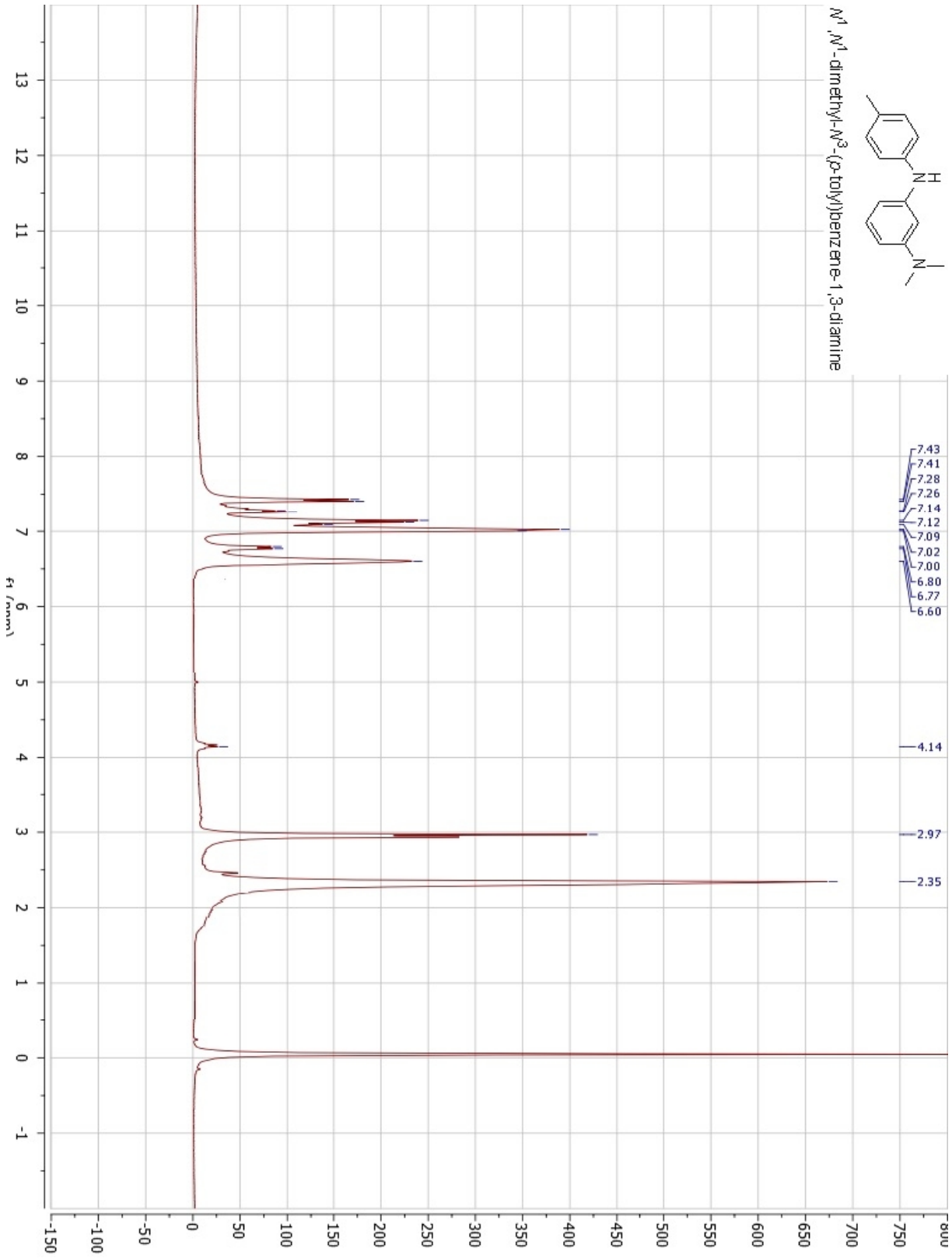

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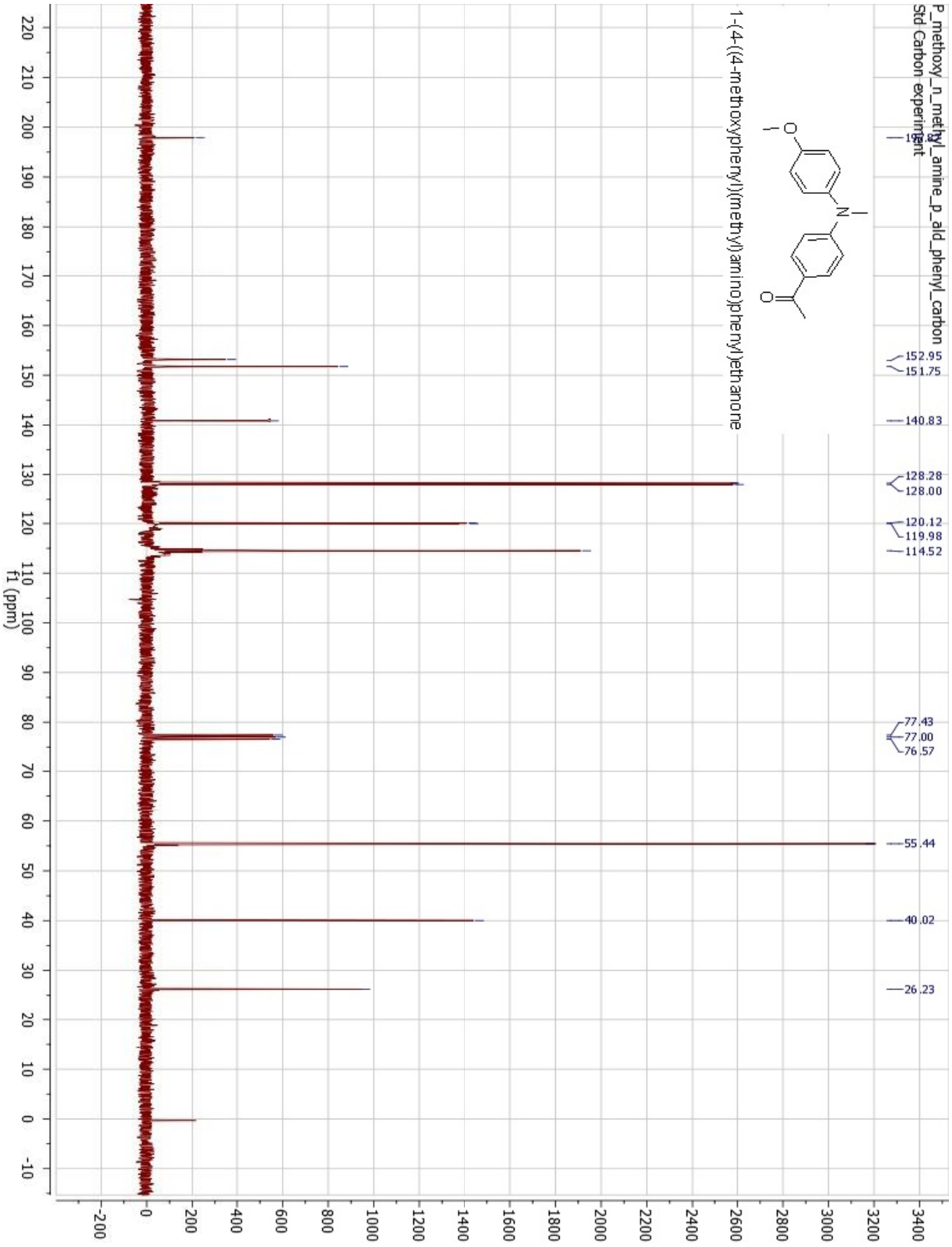

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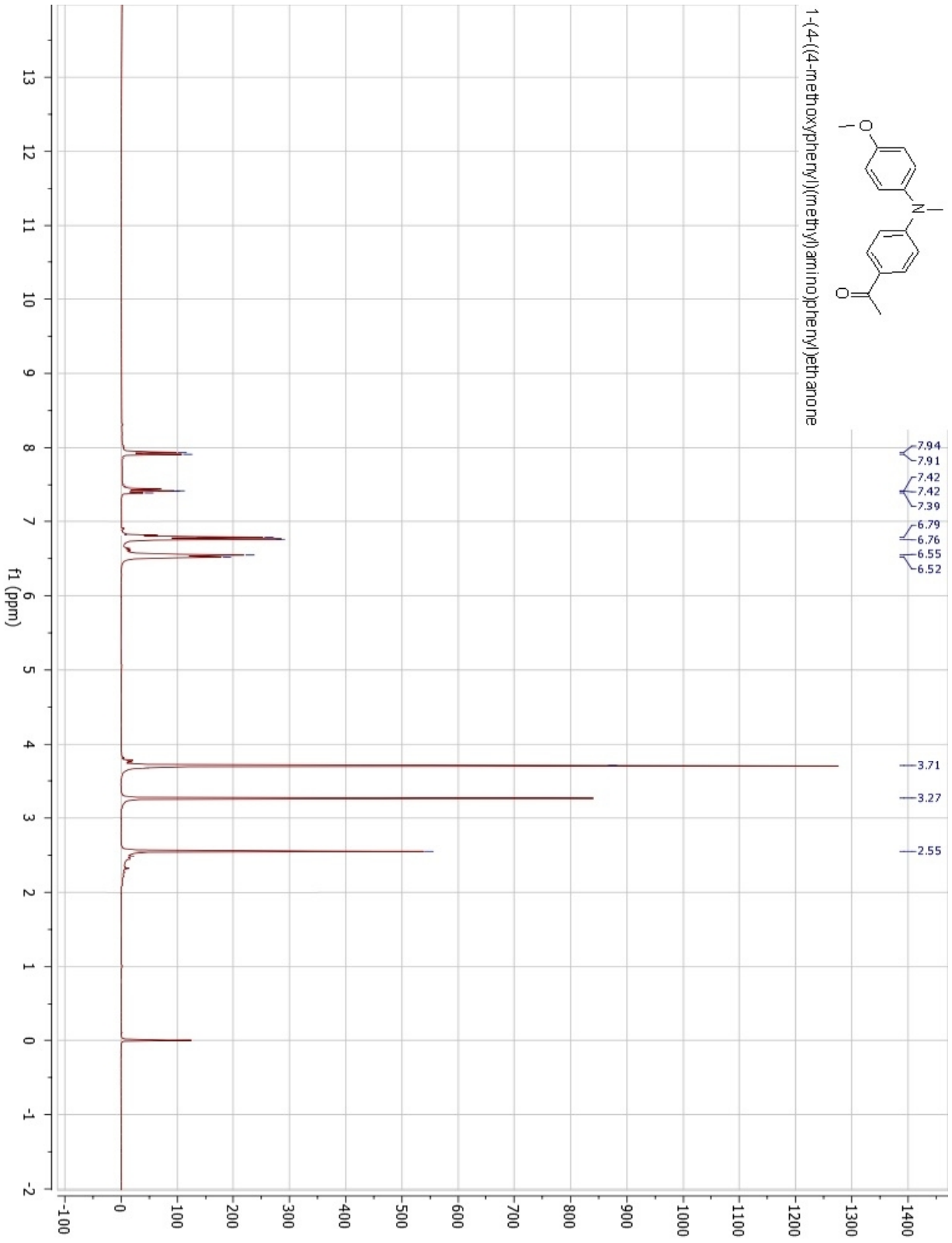

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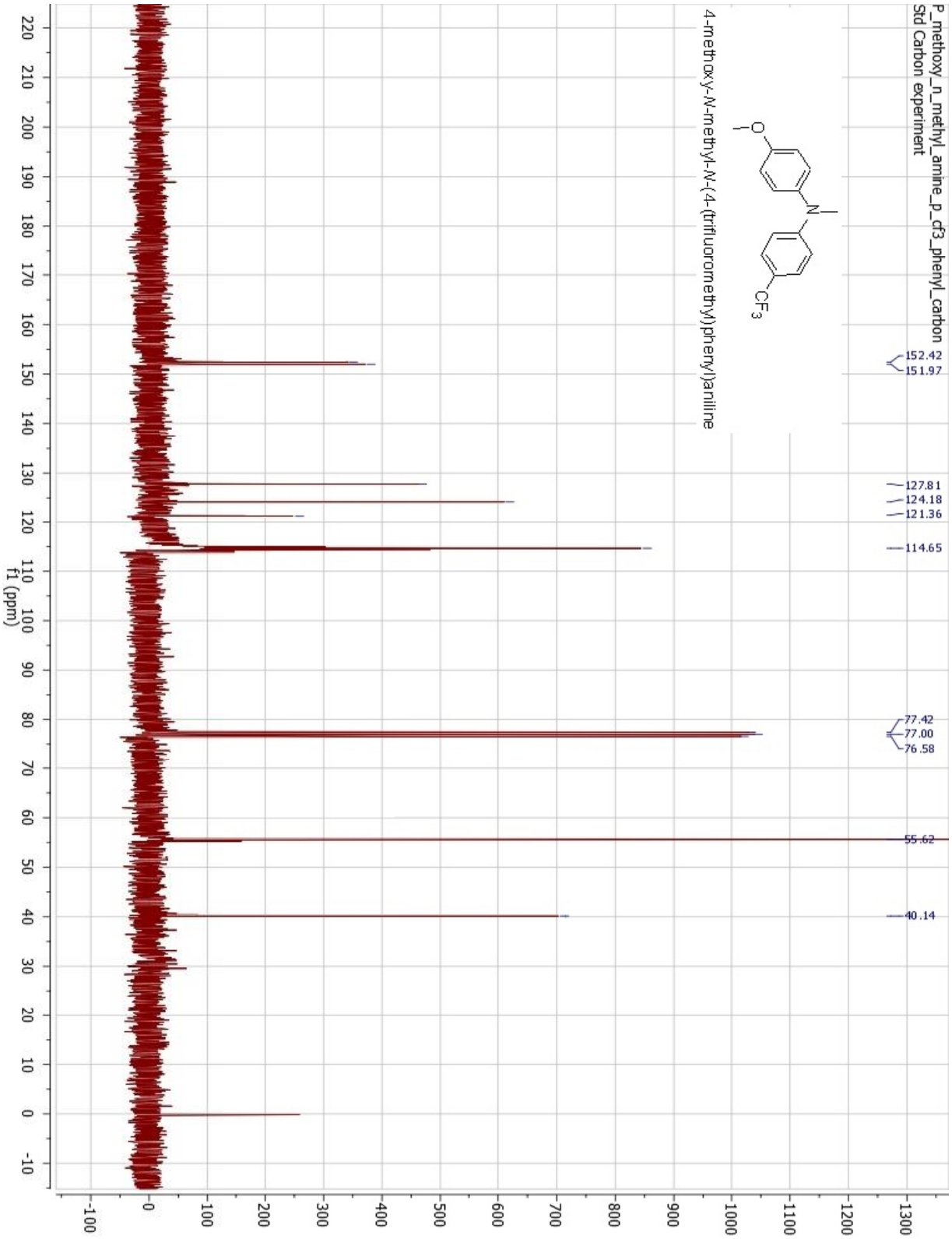

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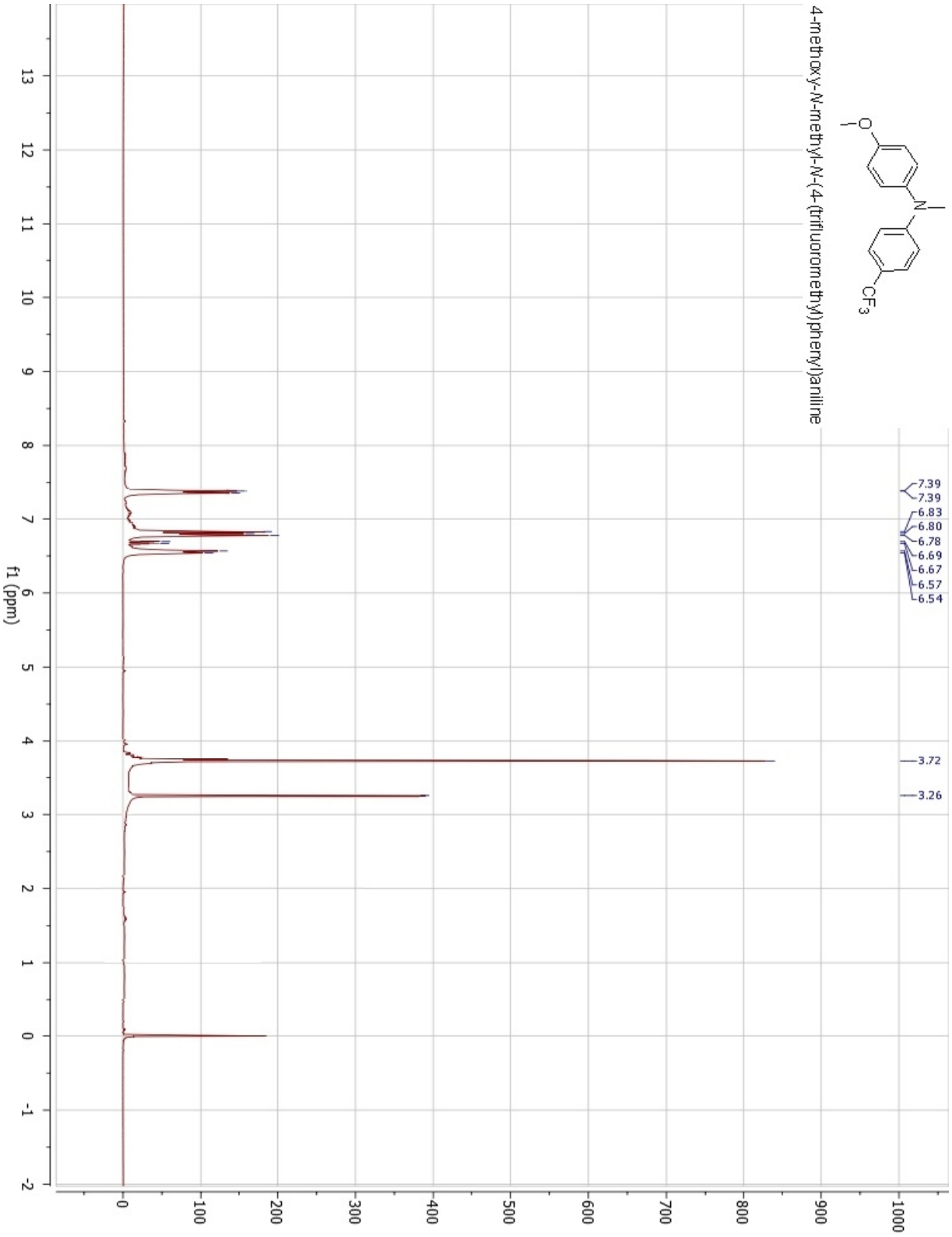

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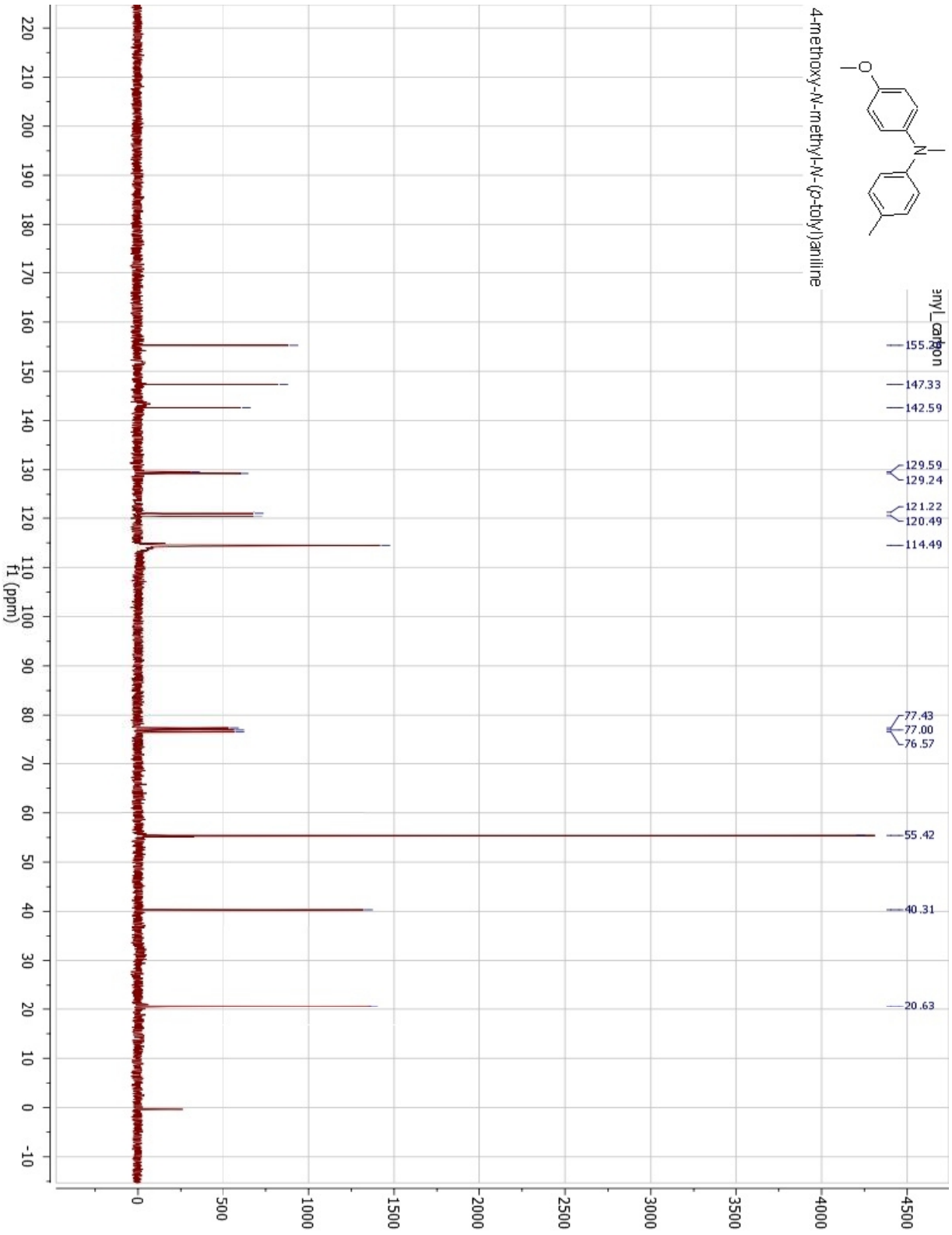

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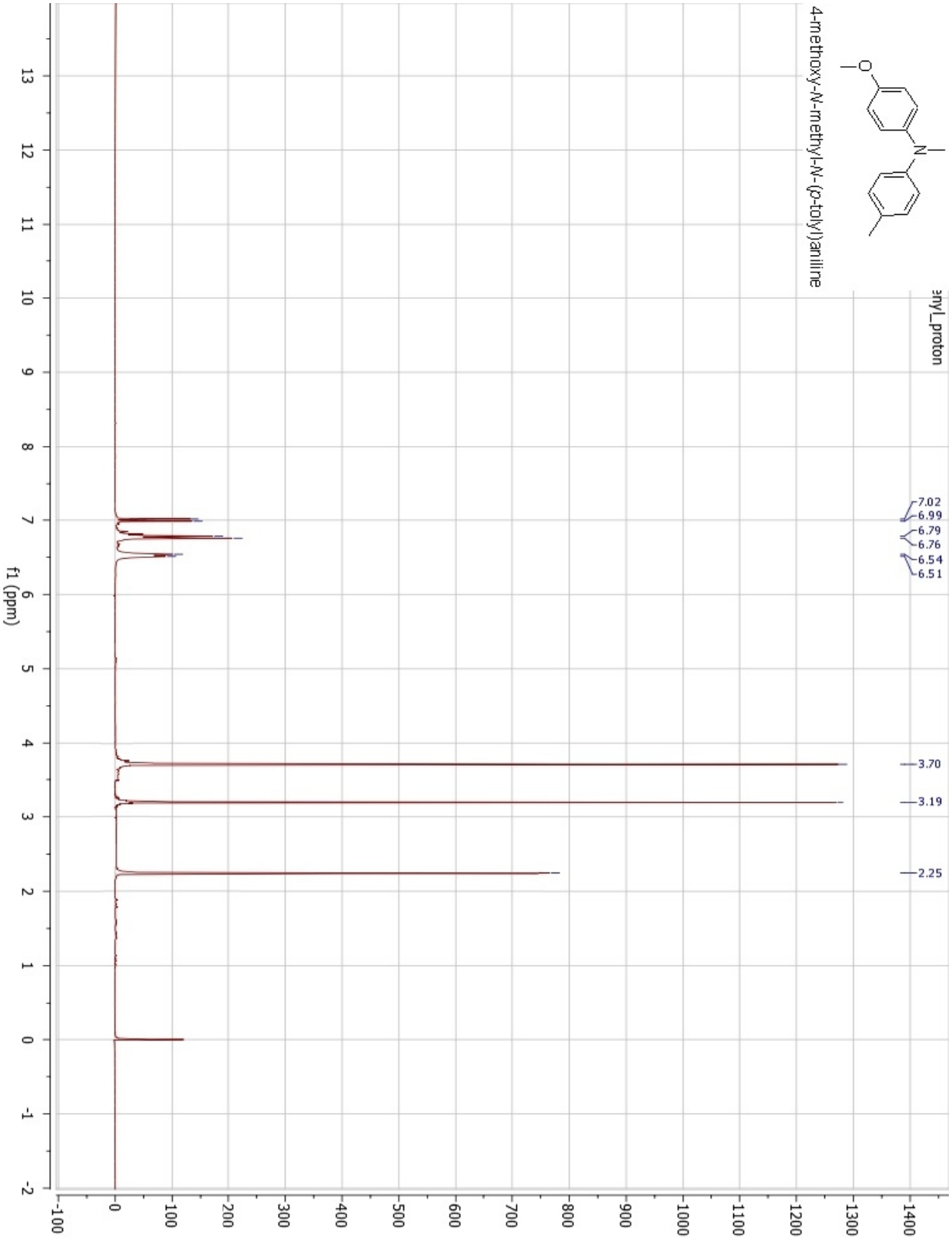

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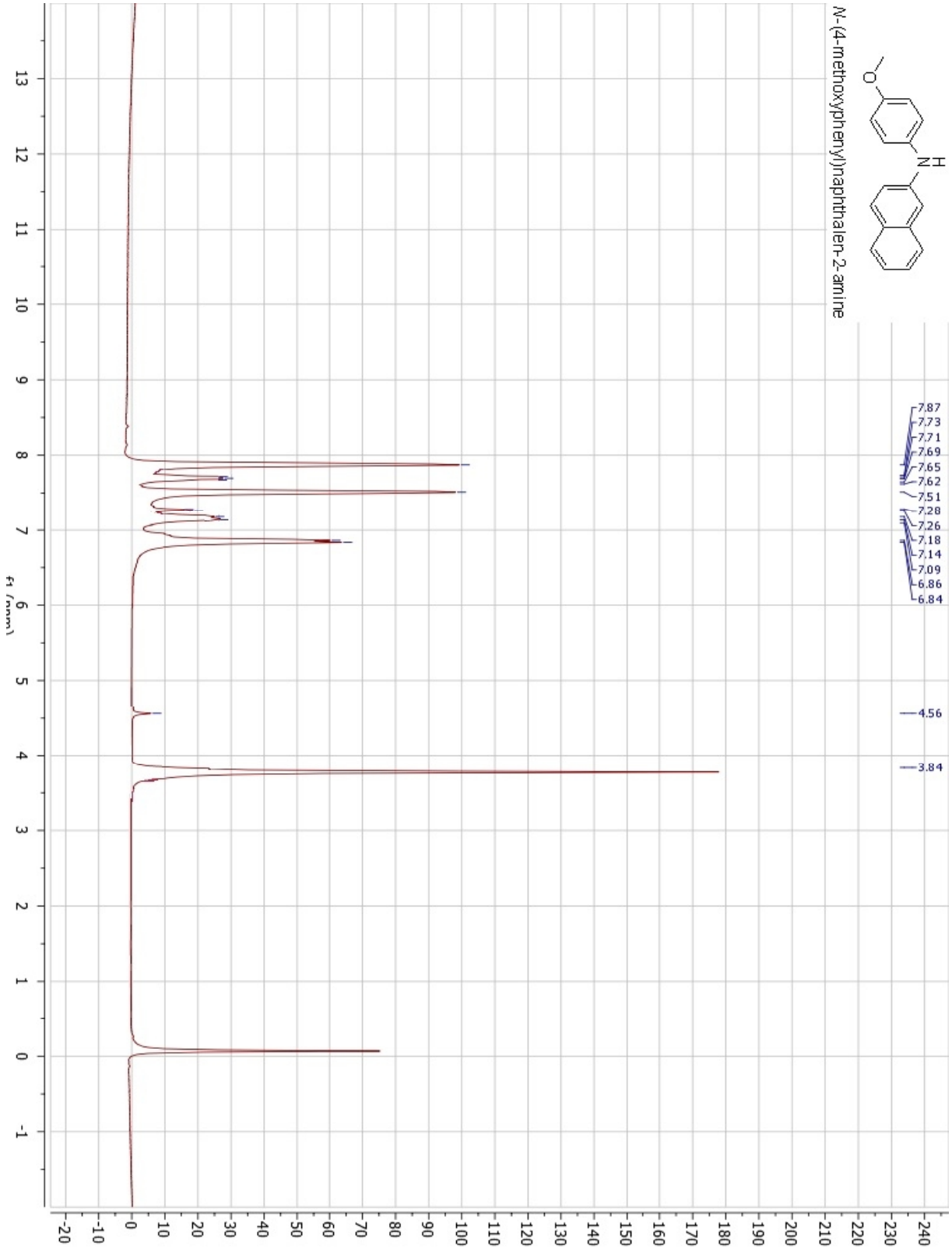

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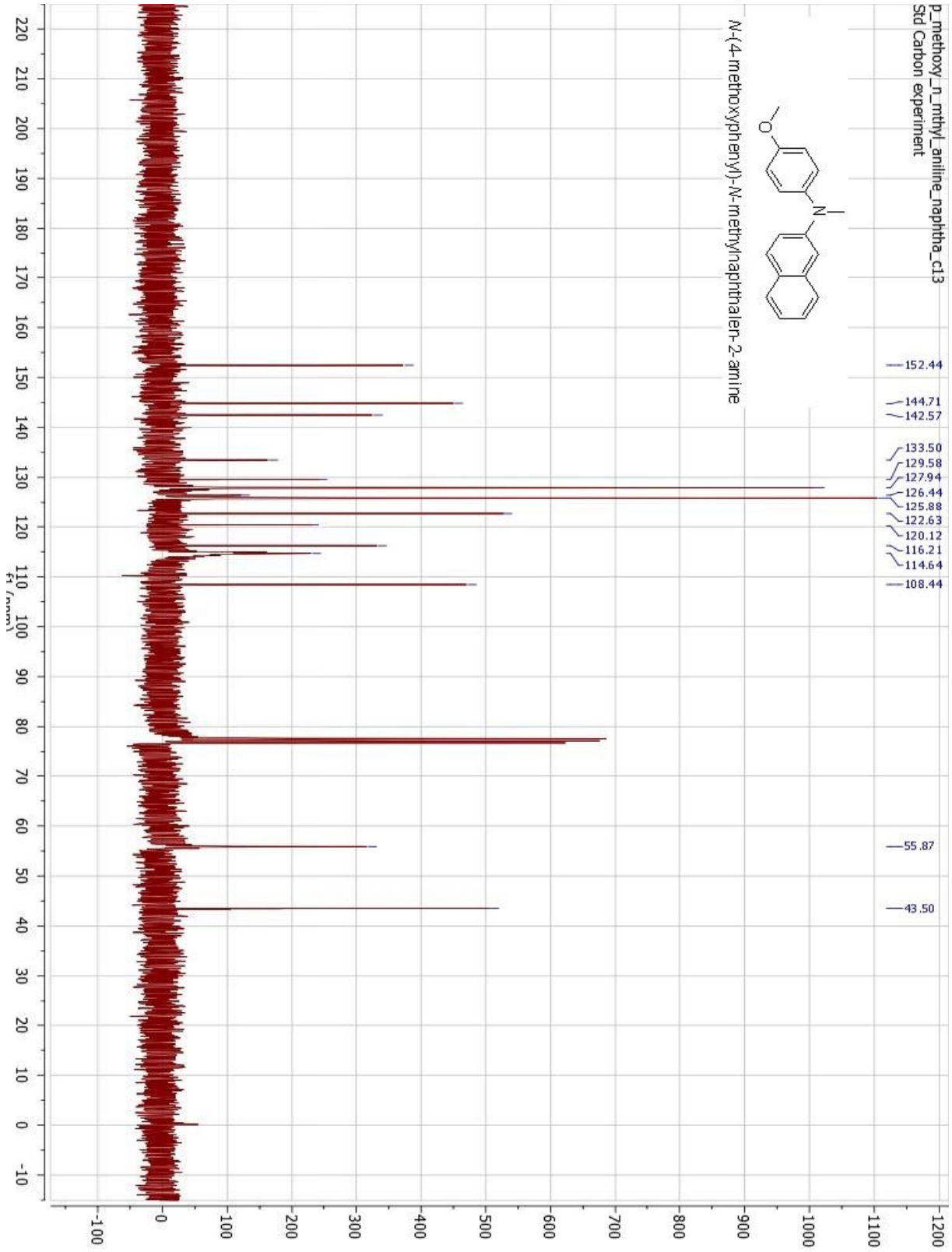

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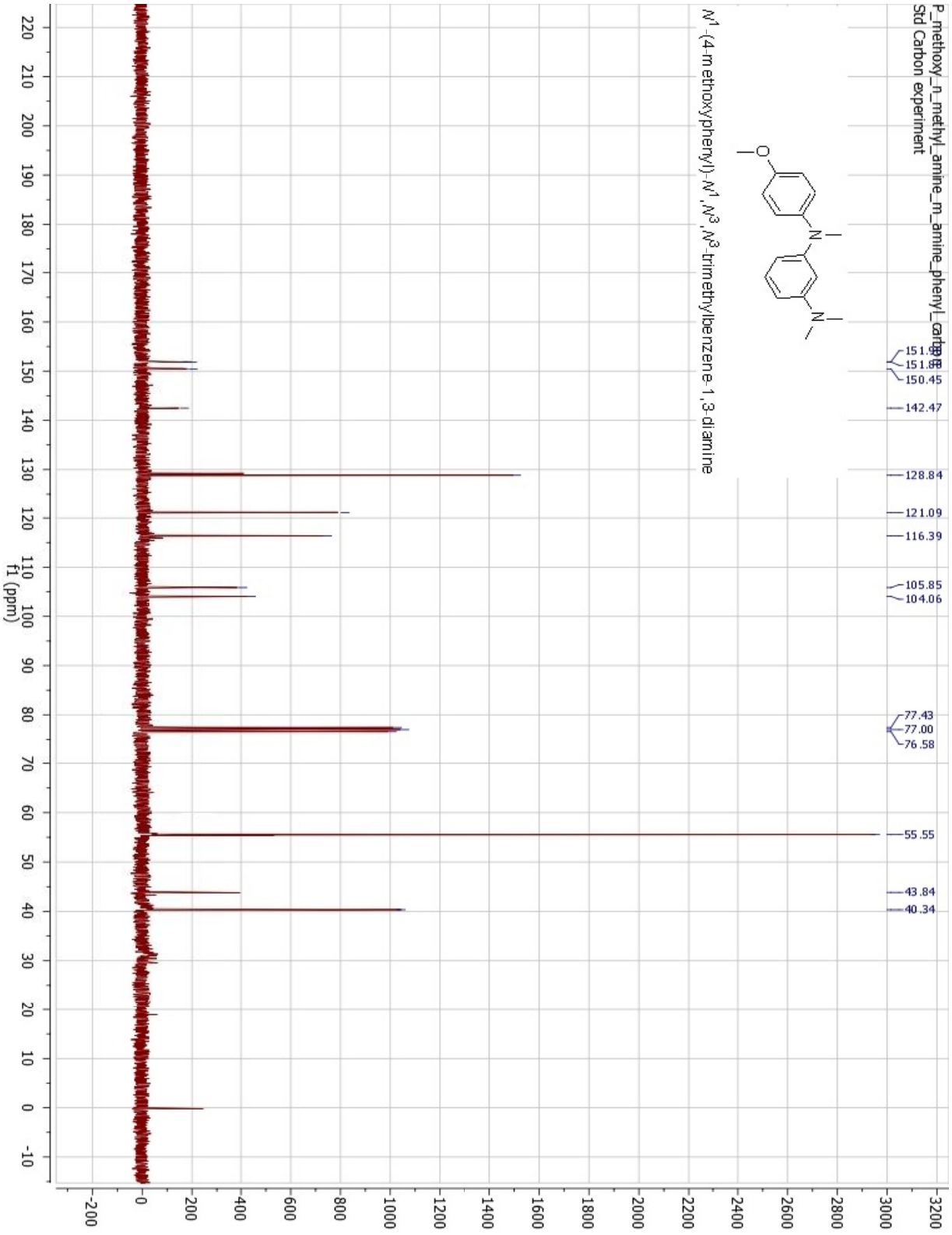

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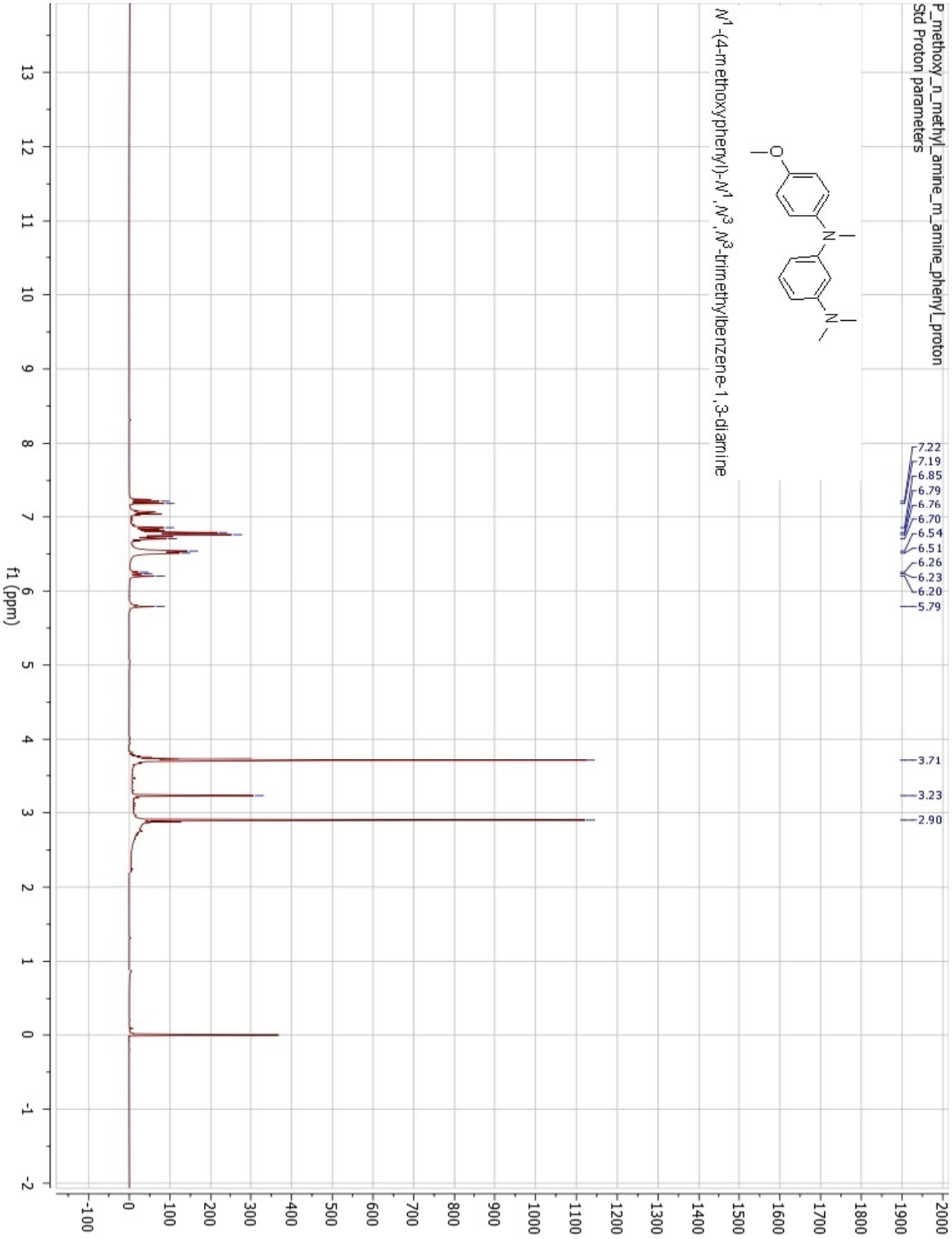

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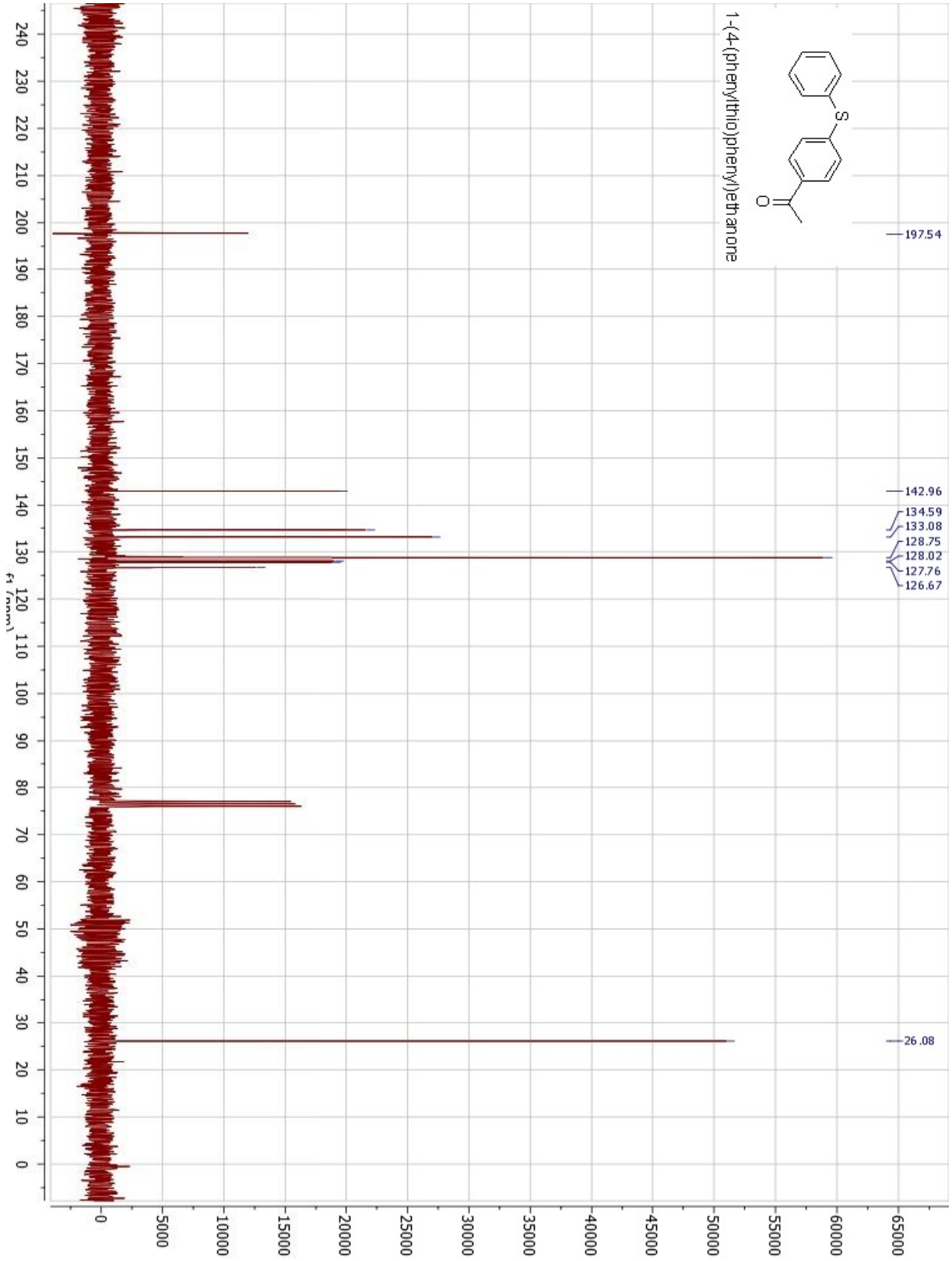

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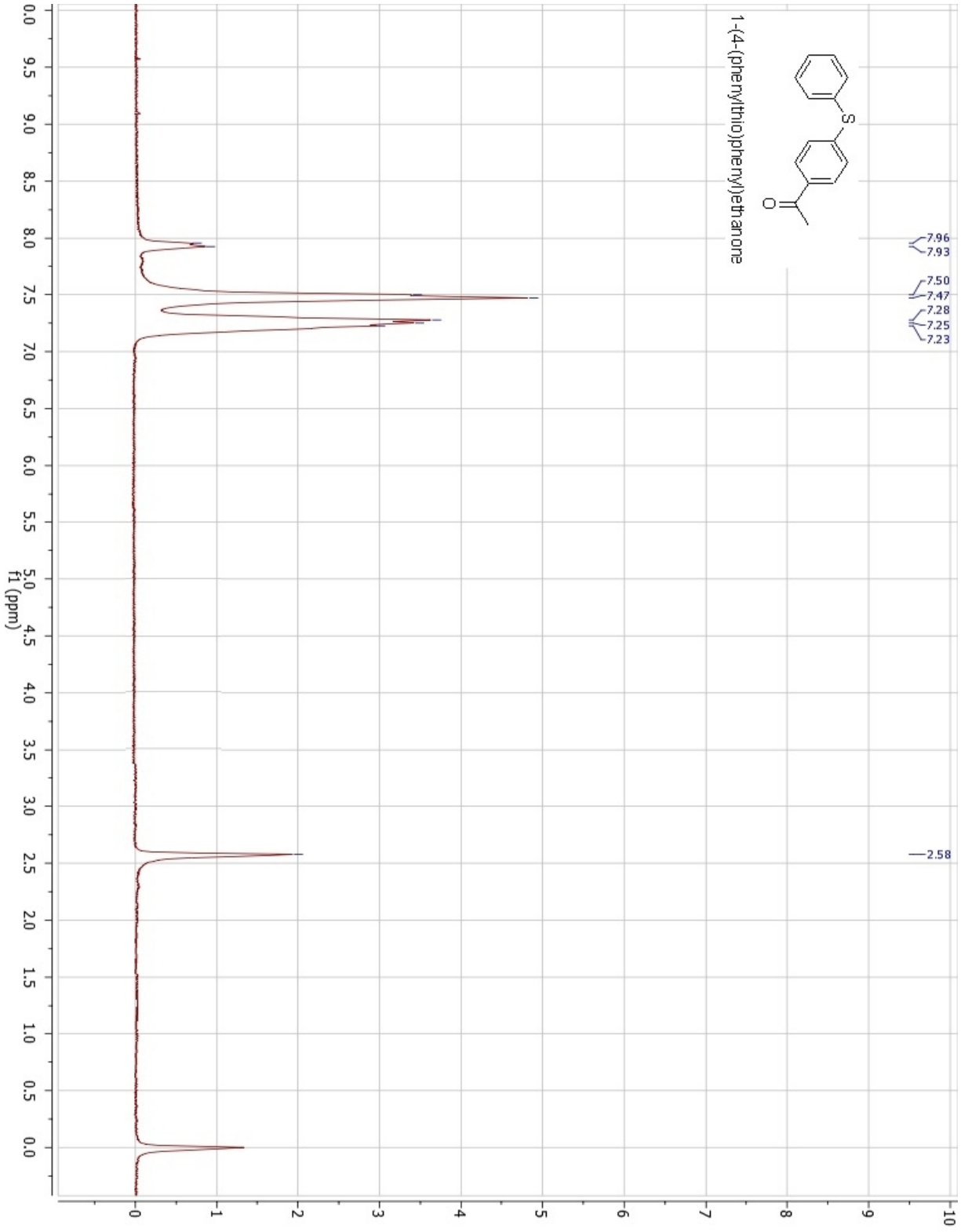

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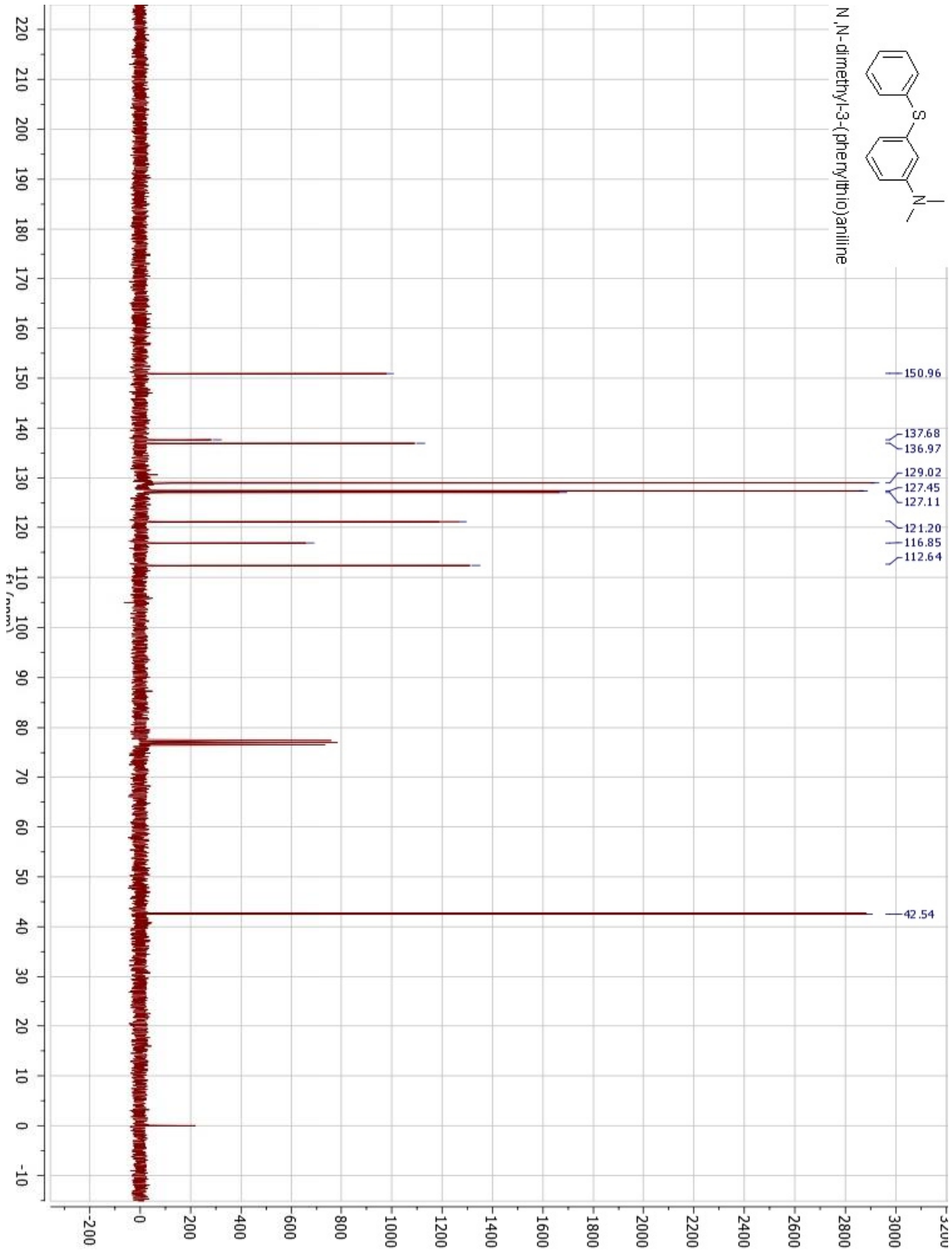

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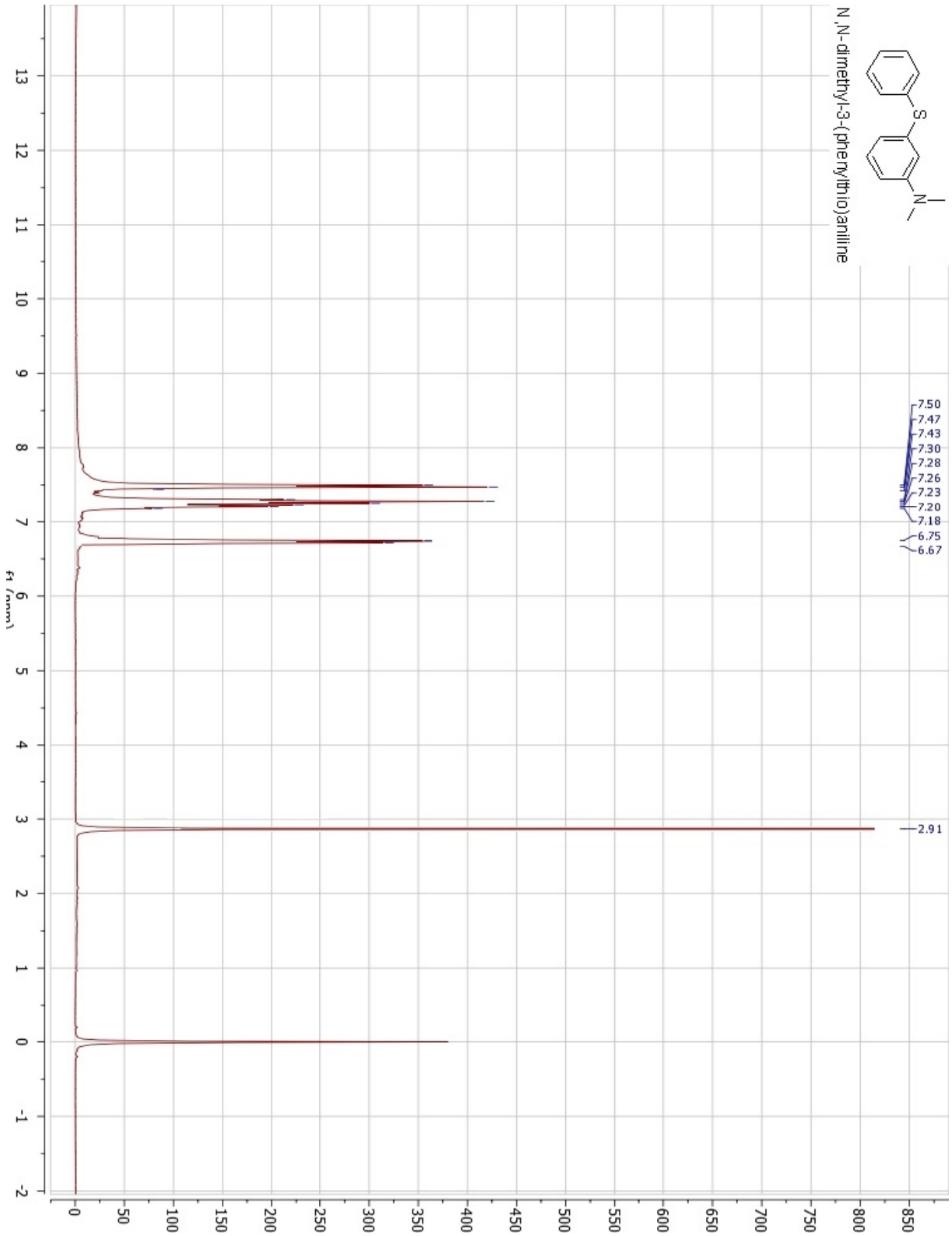

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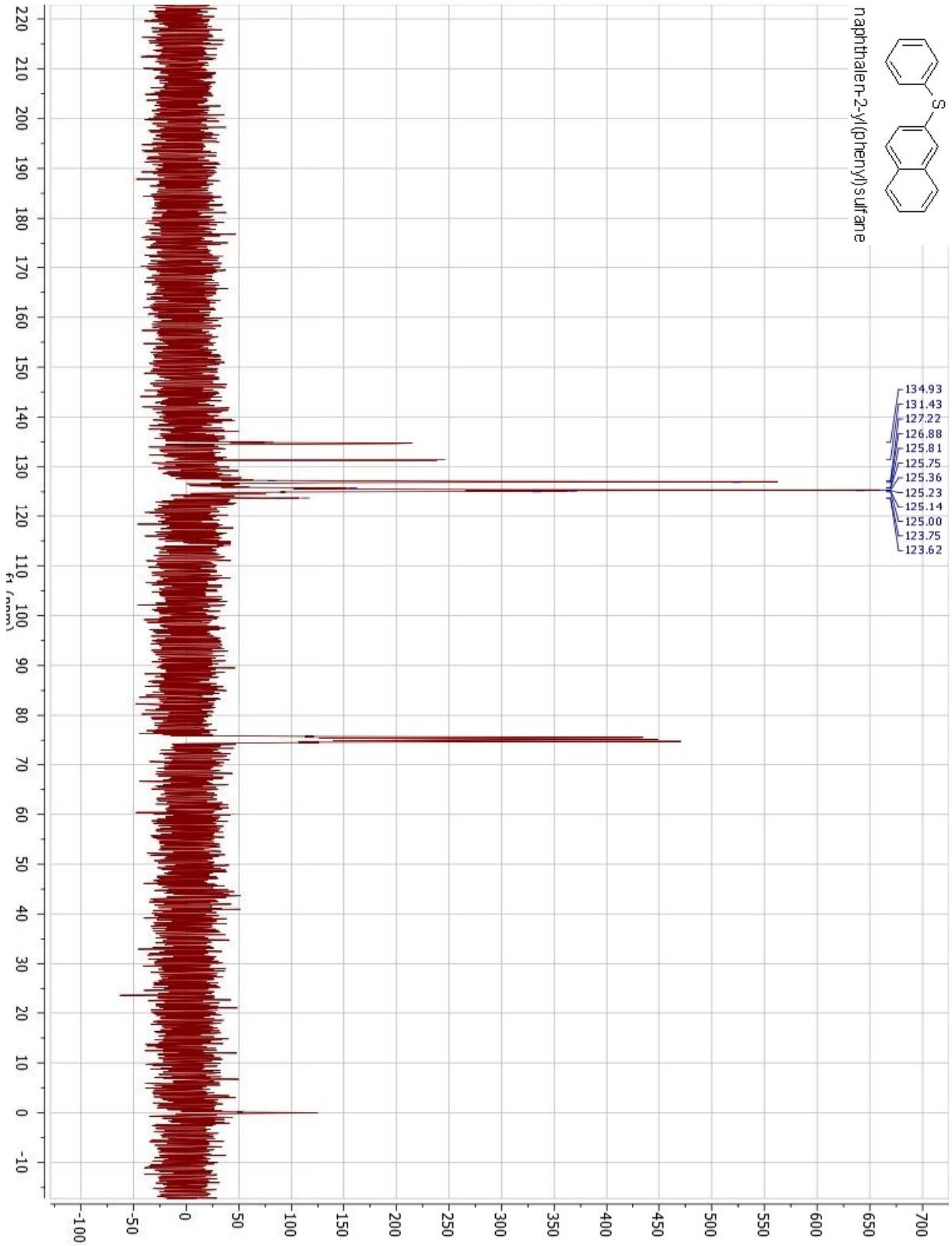

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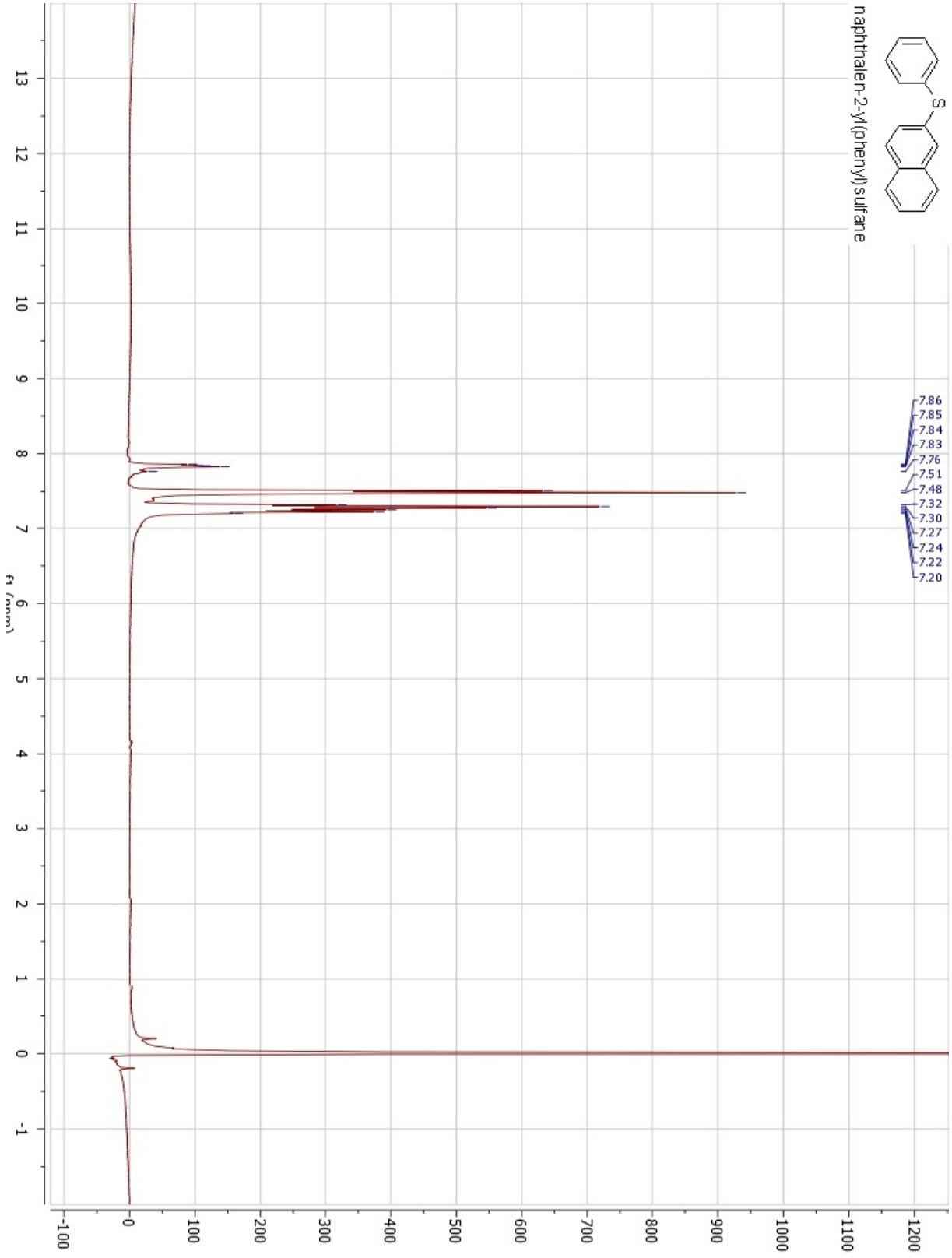

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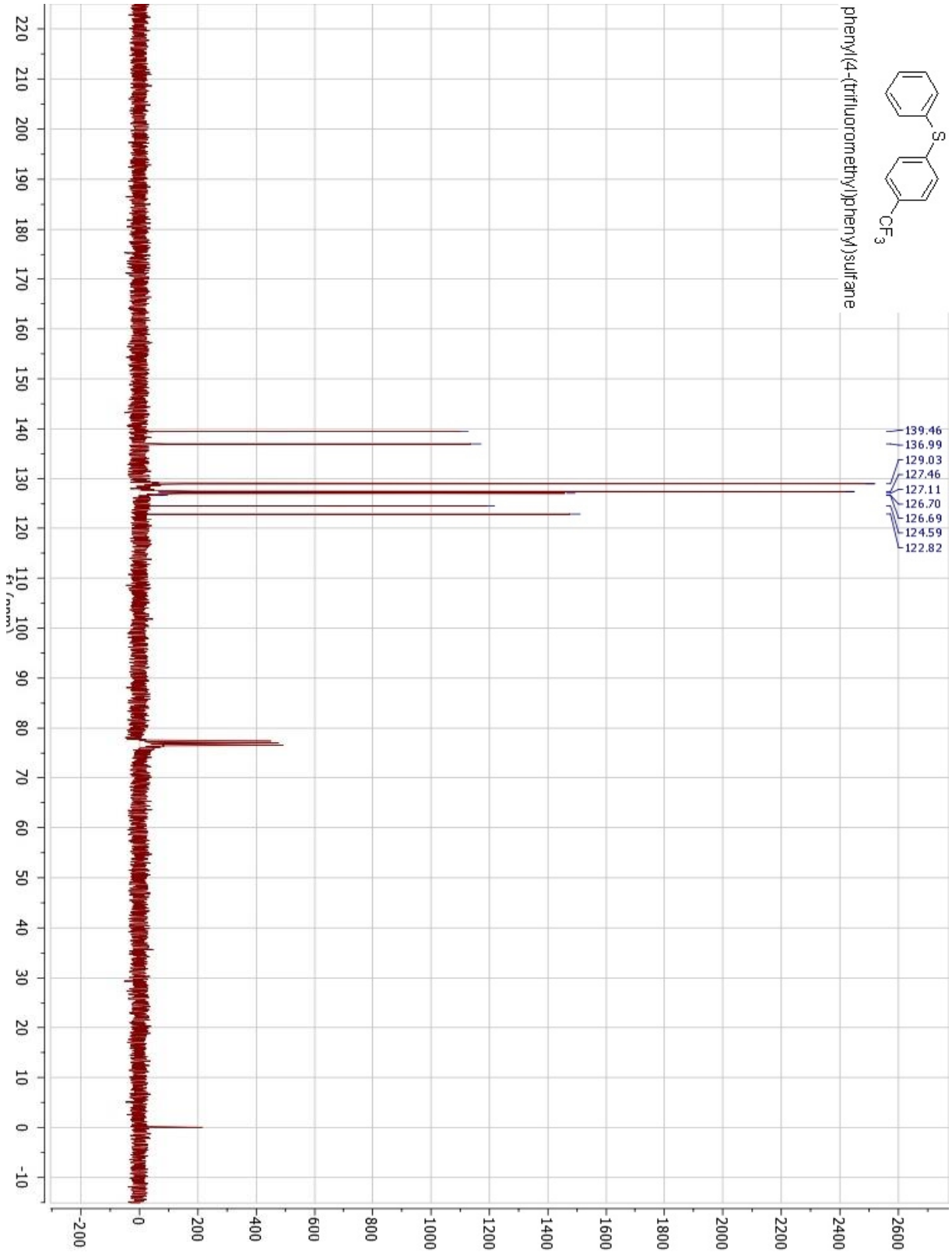

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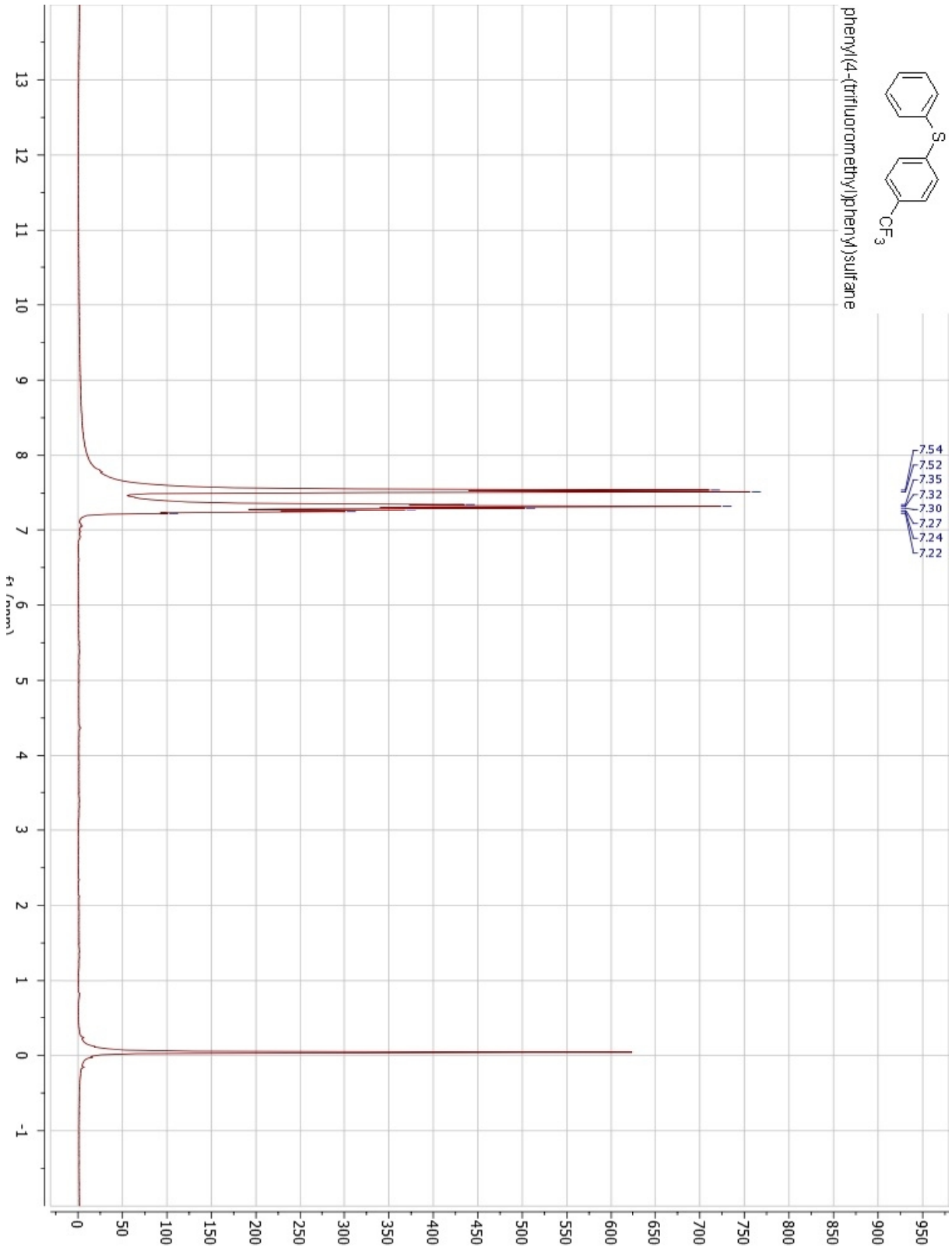
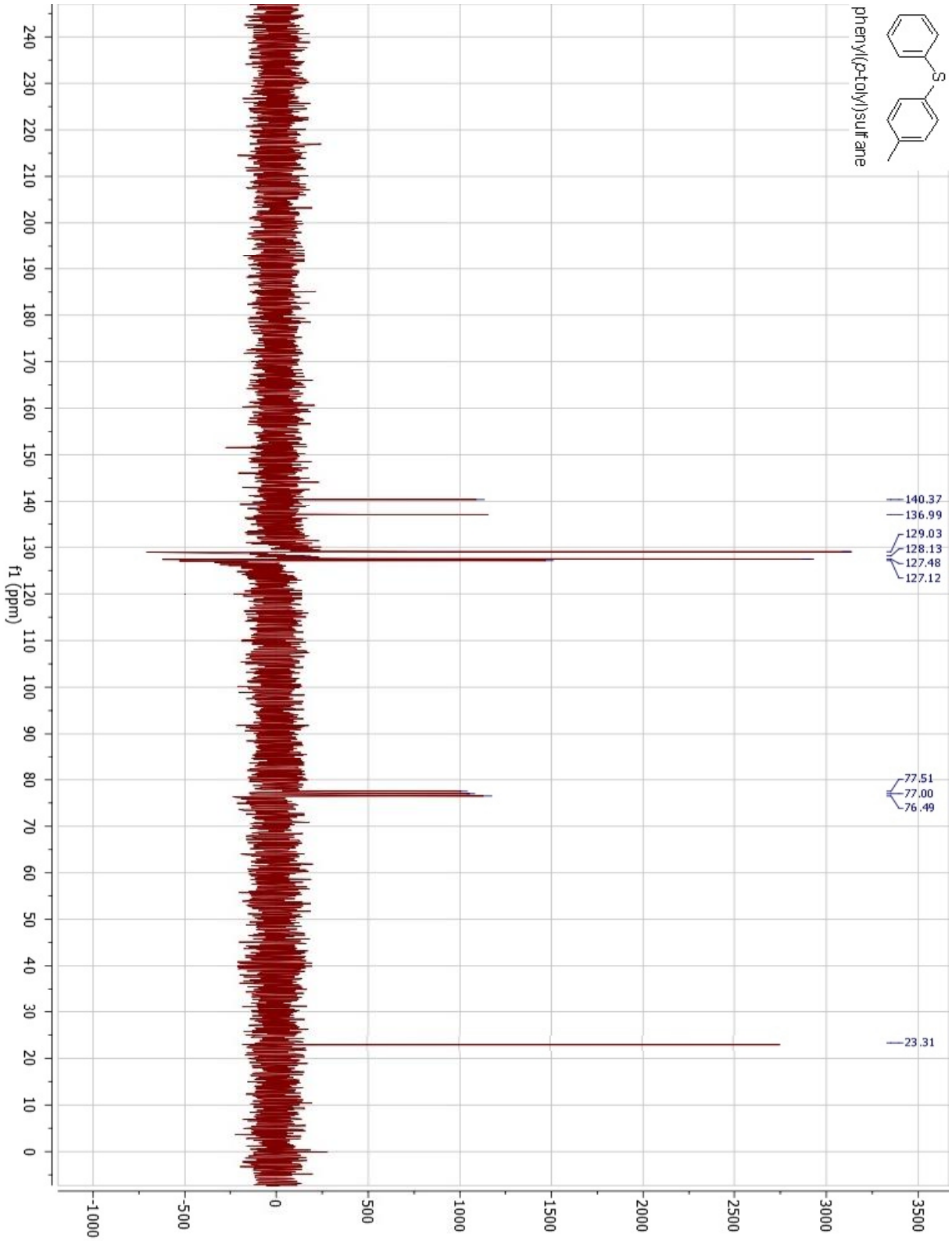


^{13}Carbon NMR



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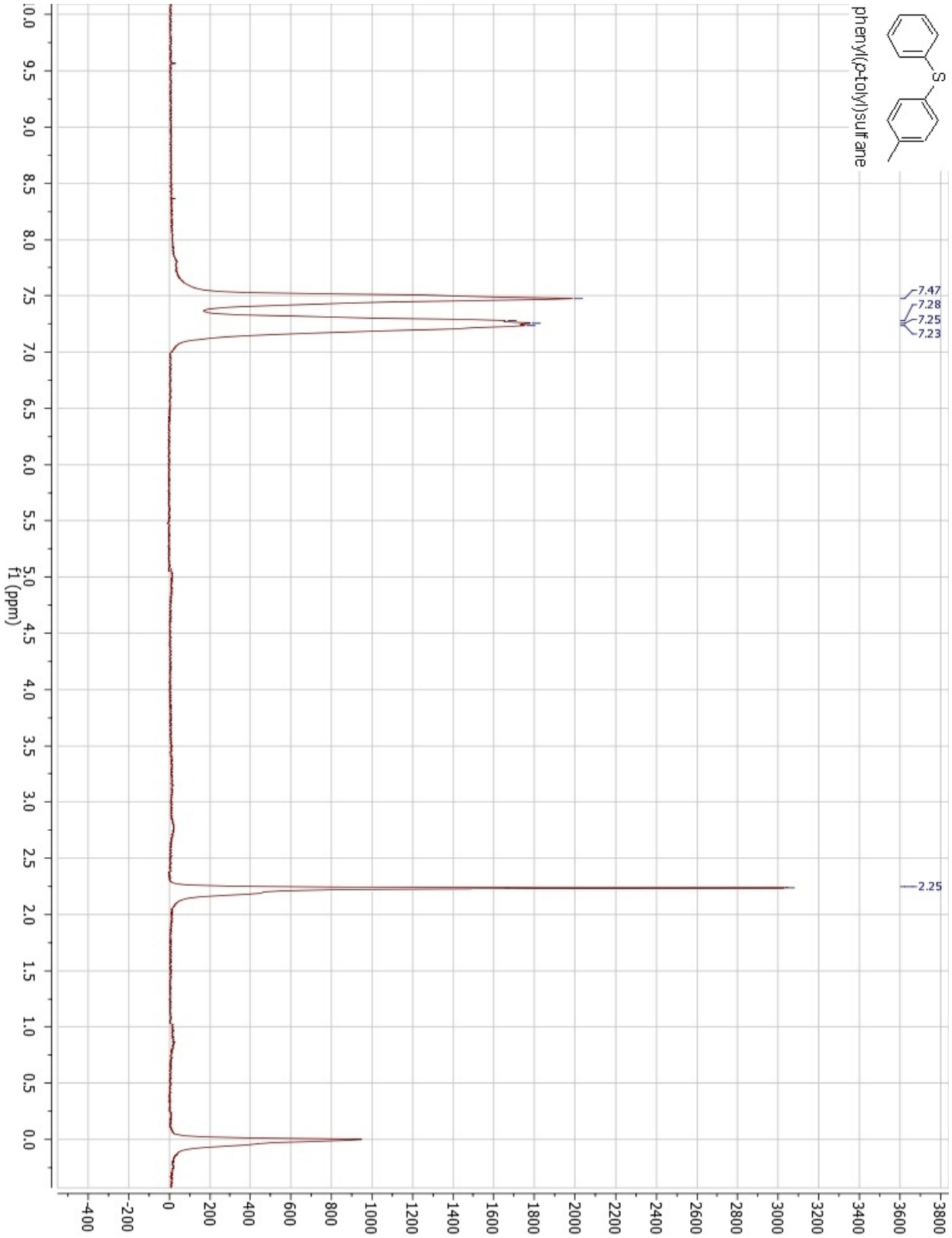

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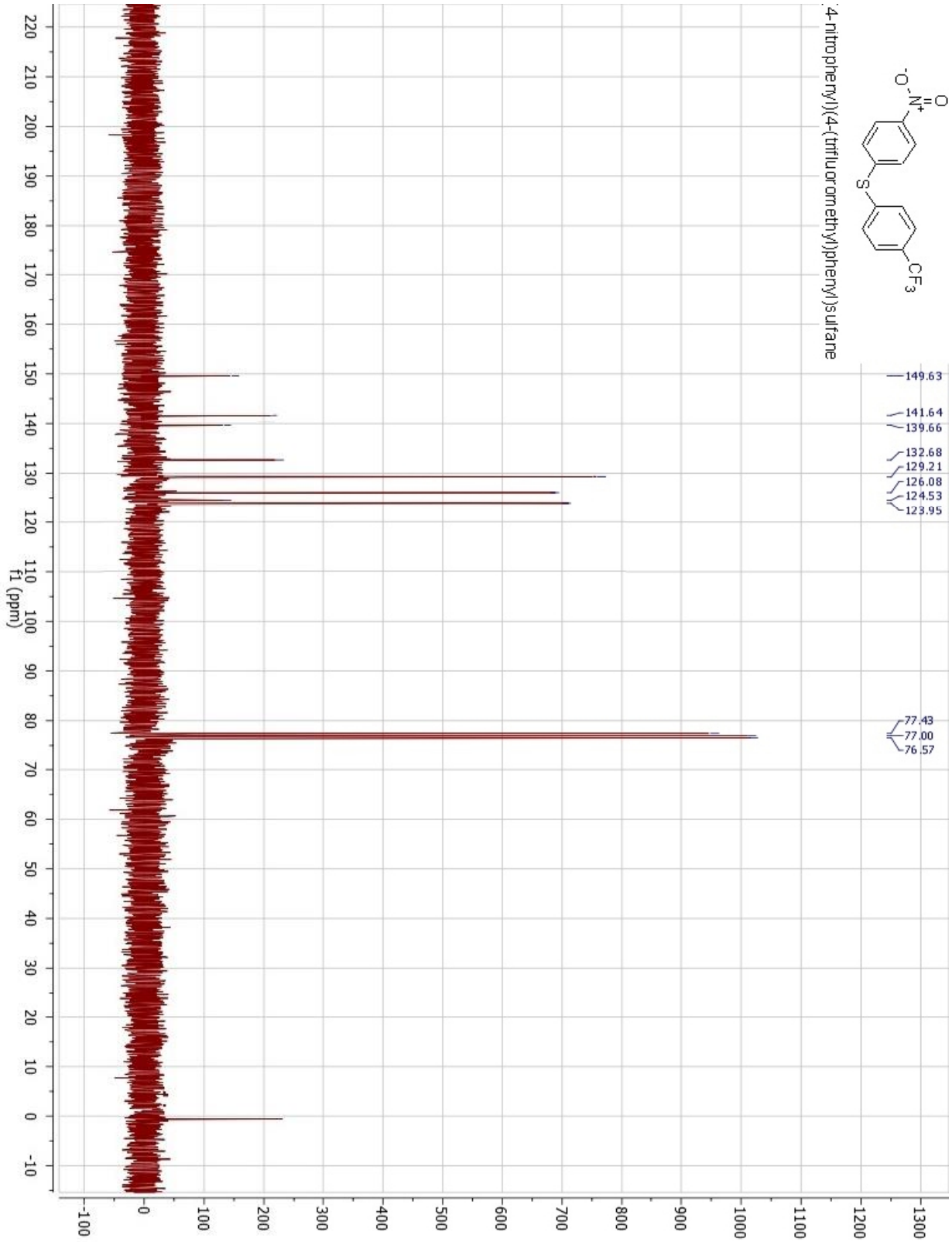

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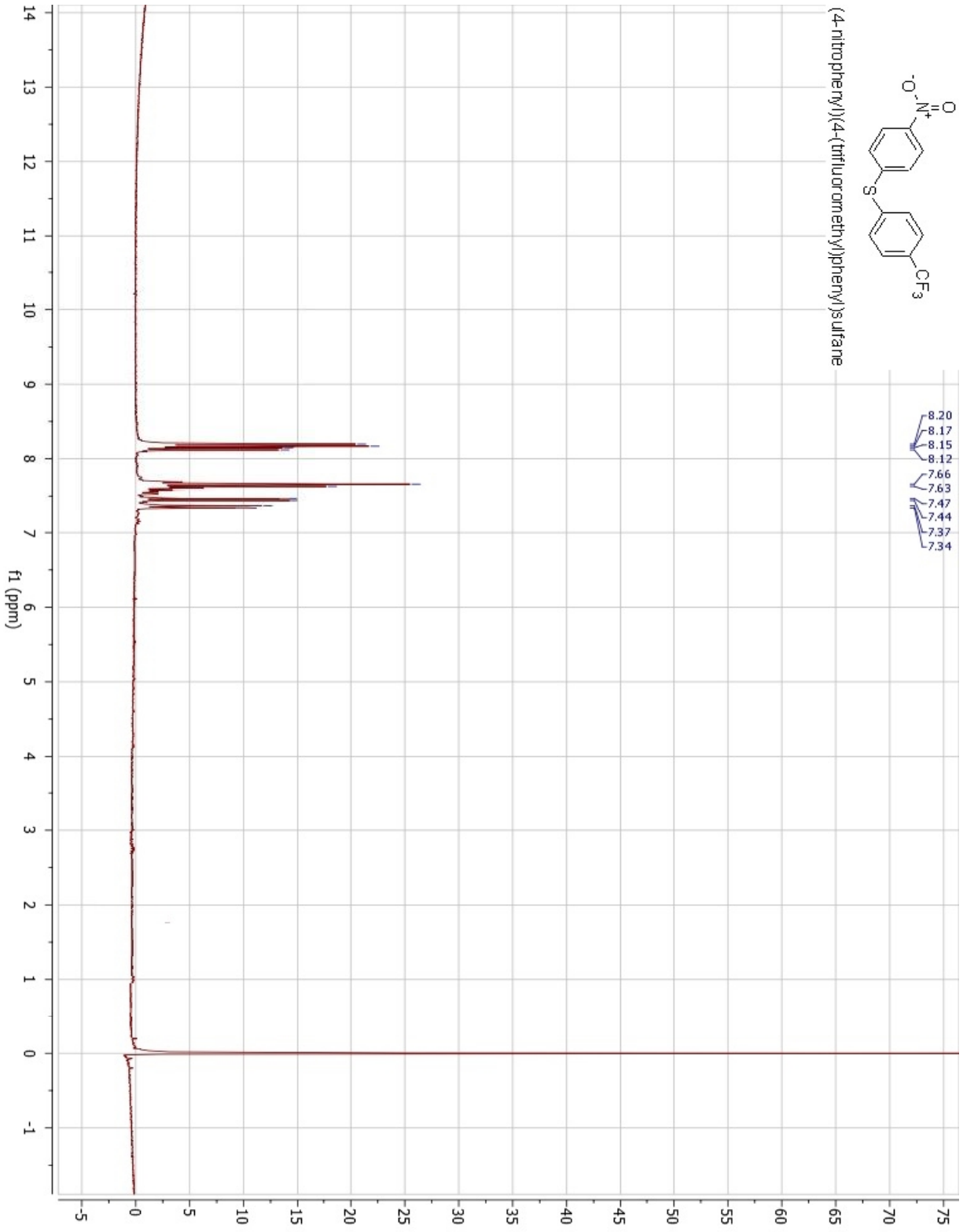

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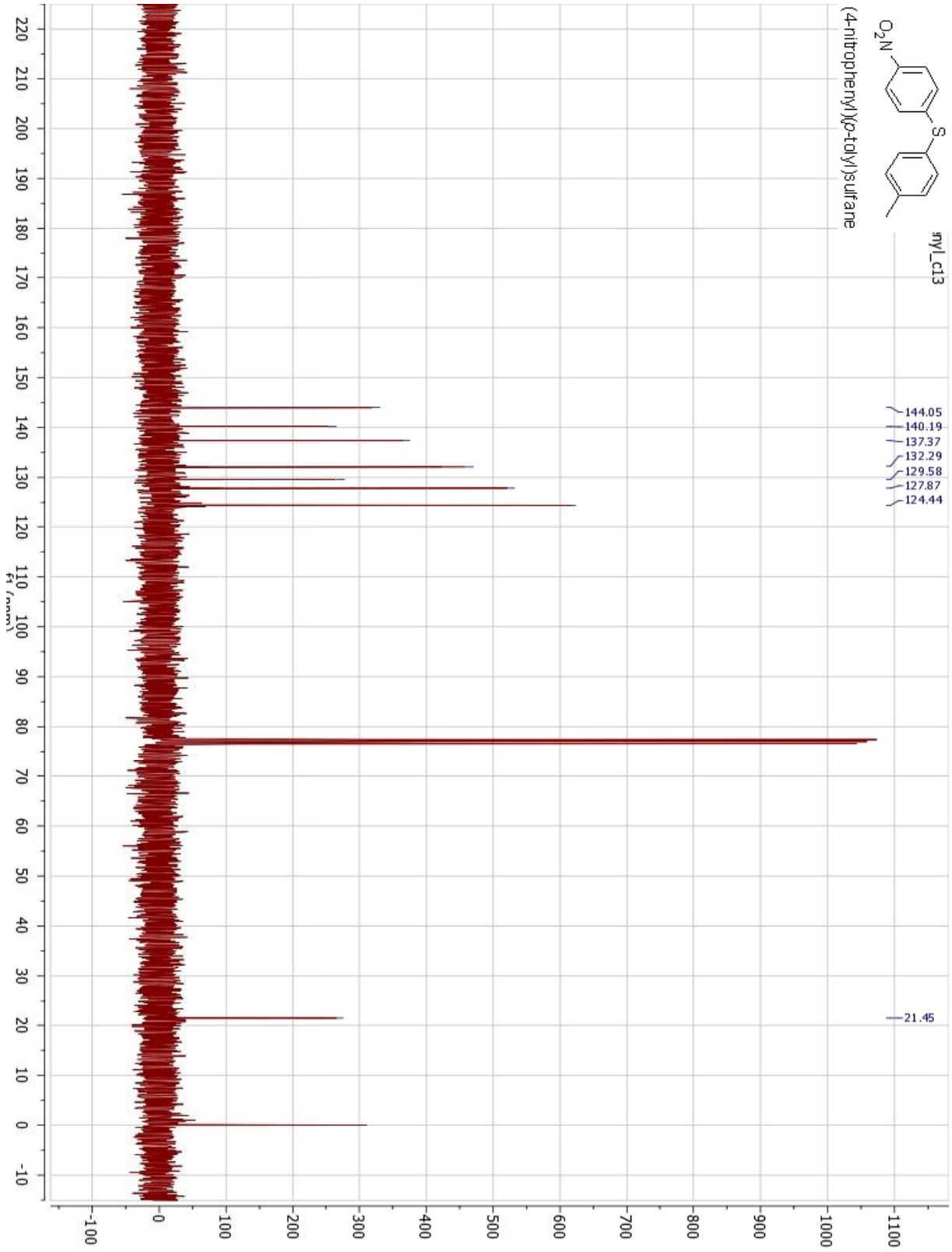

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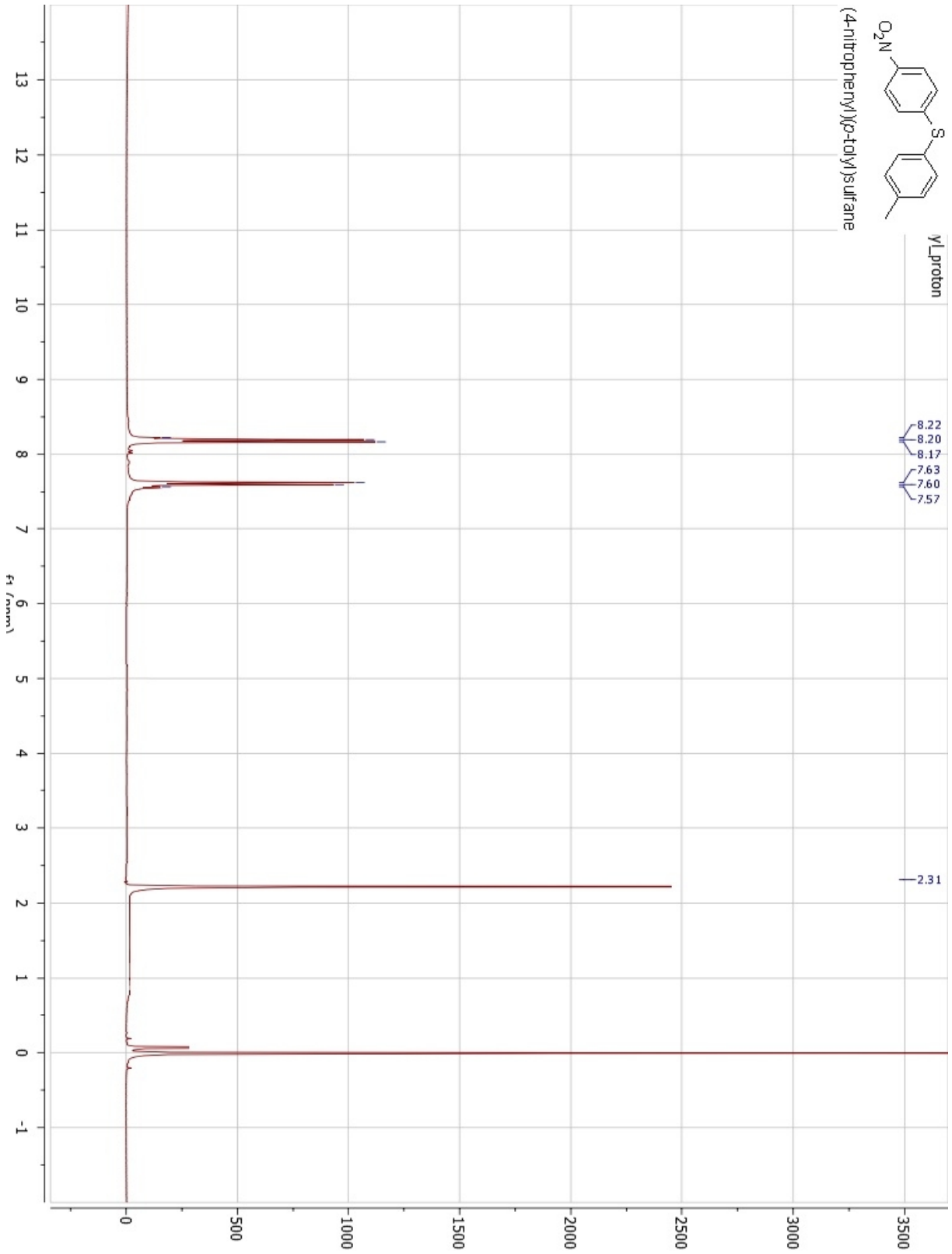

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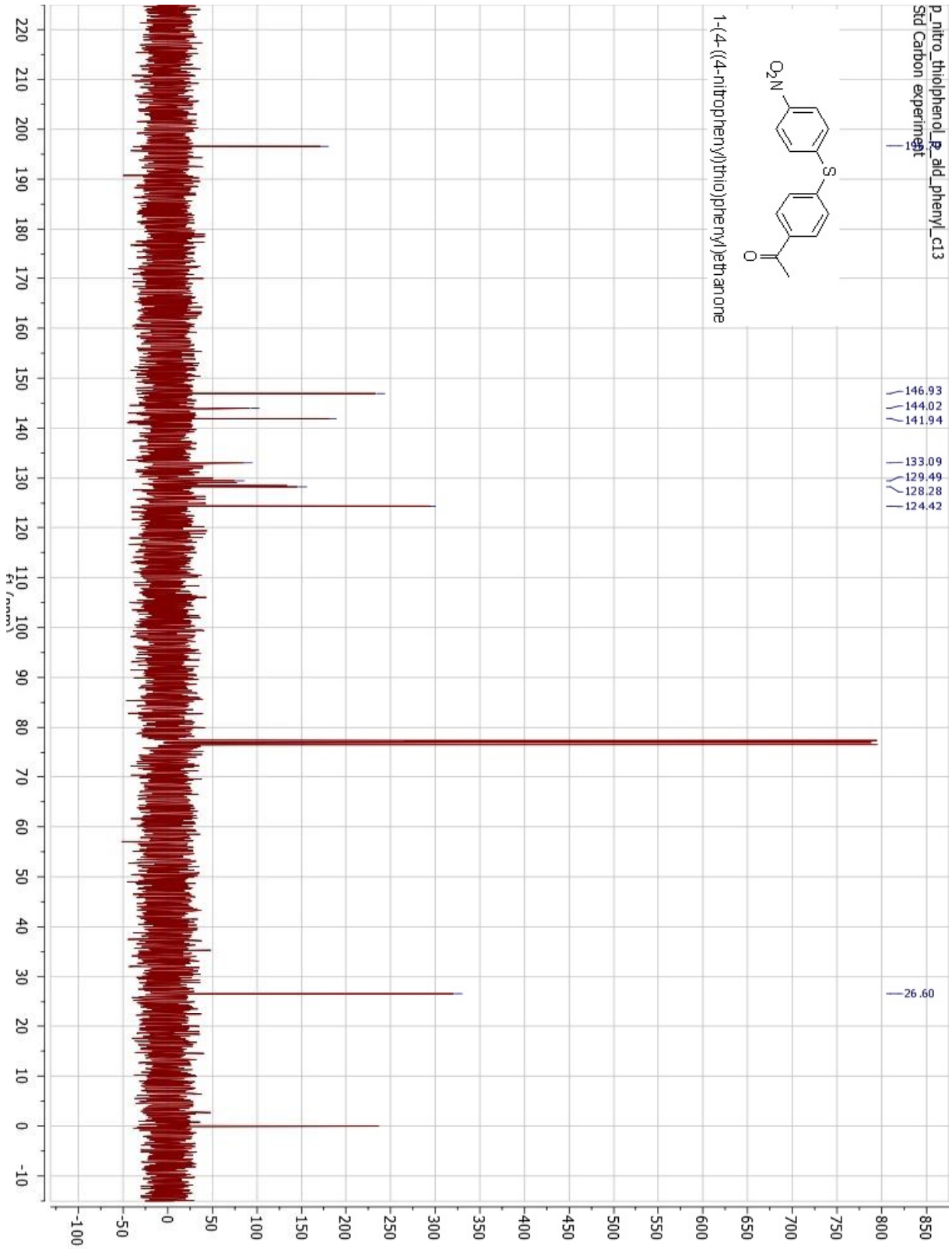

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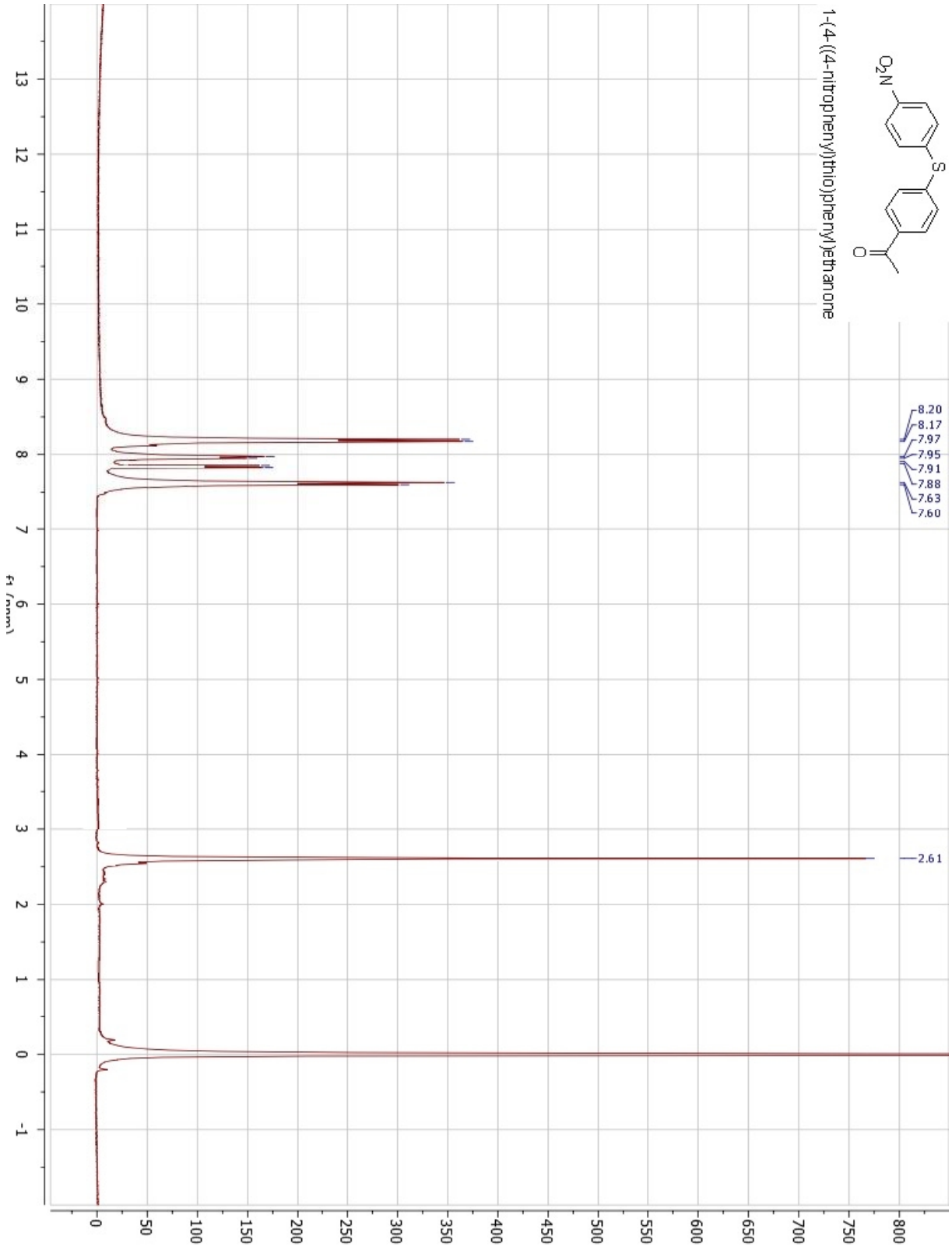

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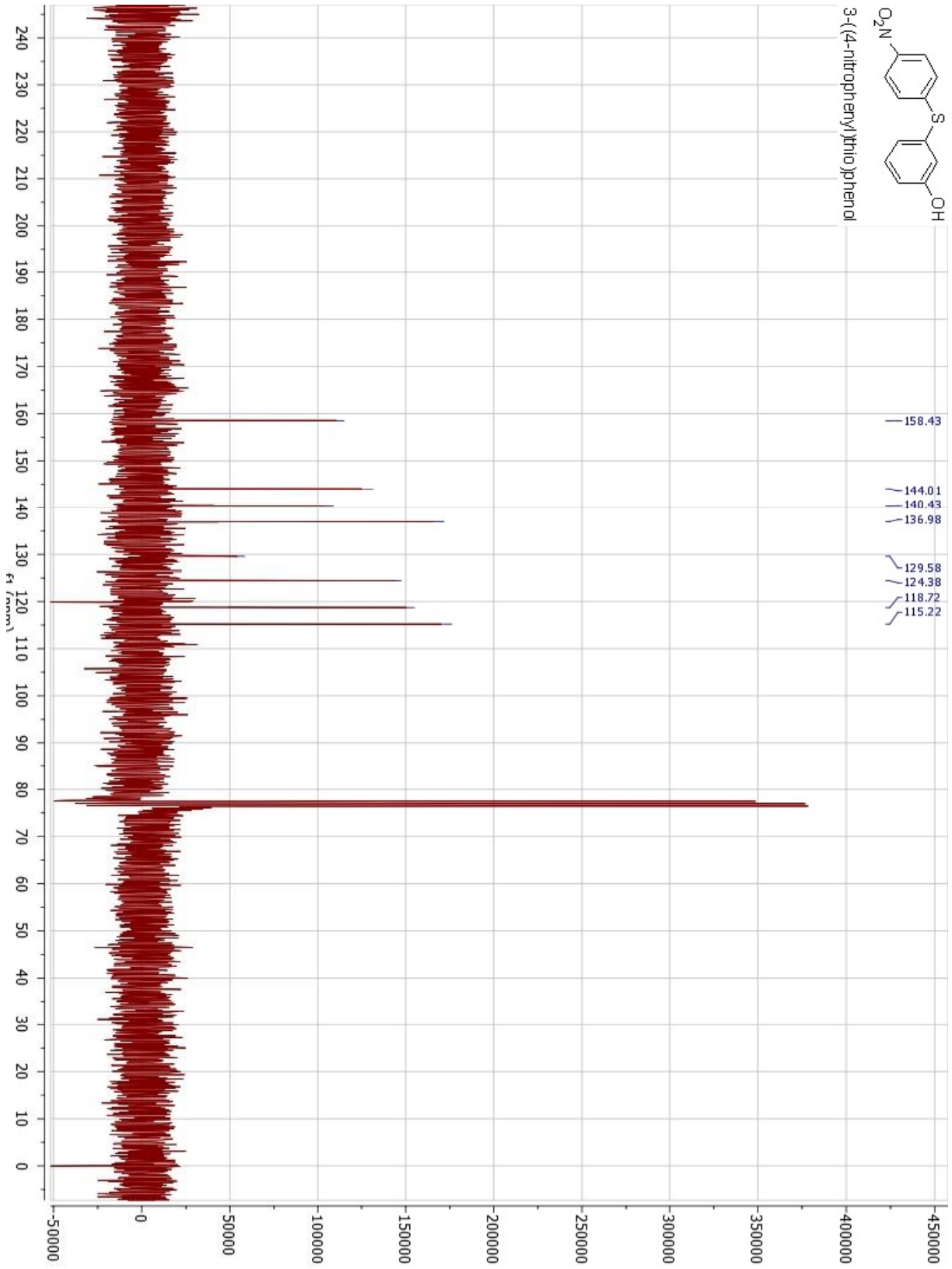

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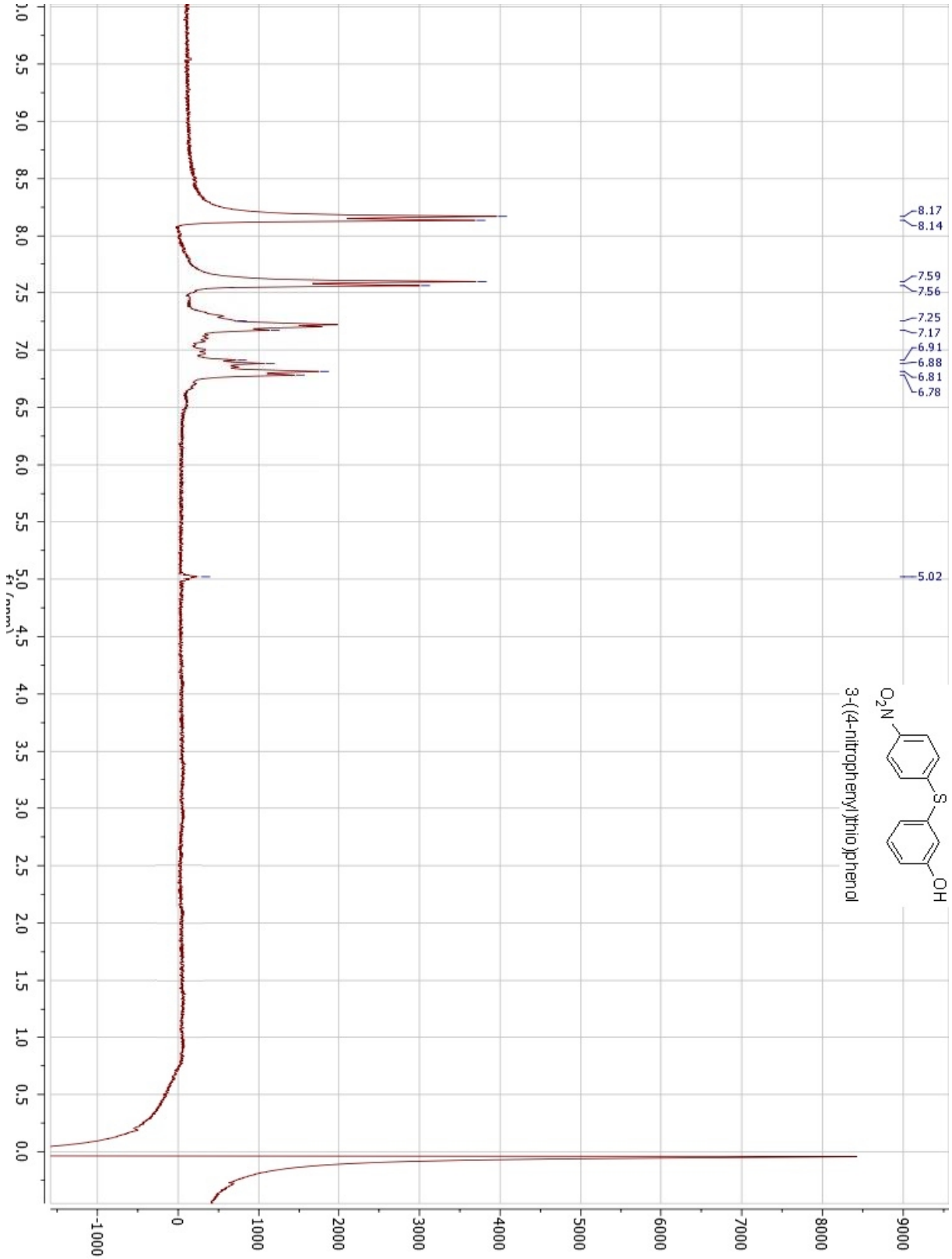

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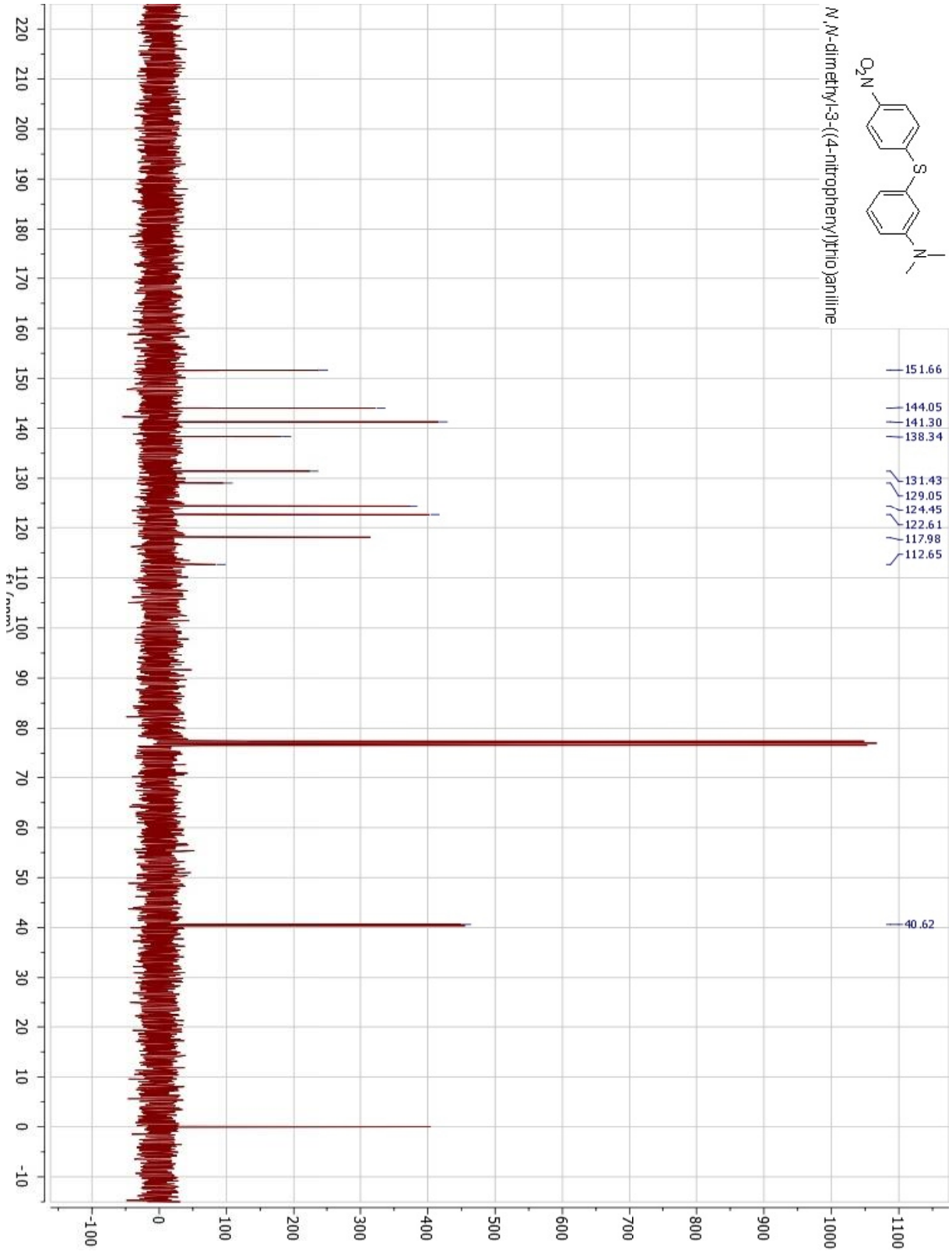

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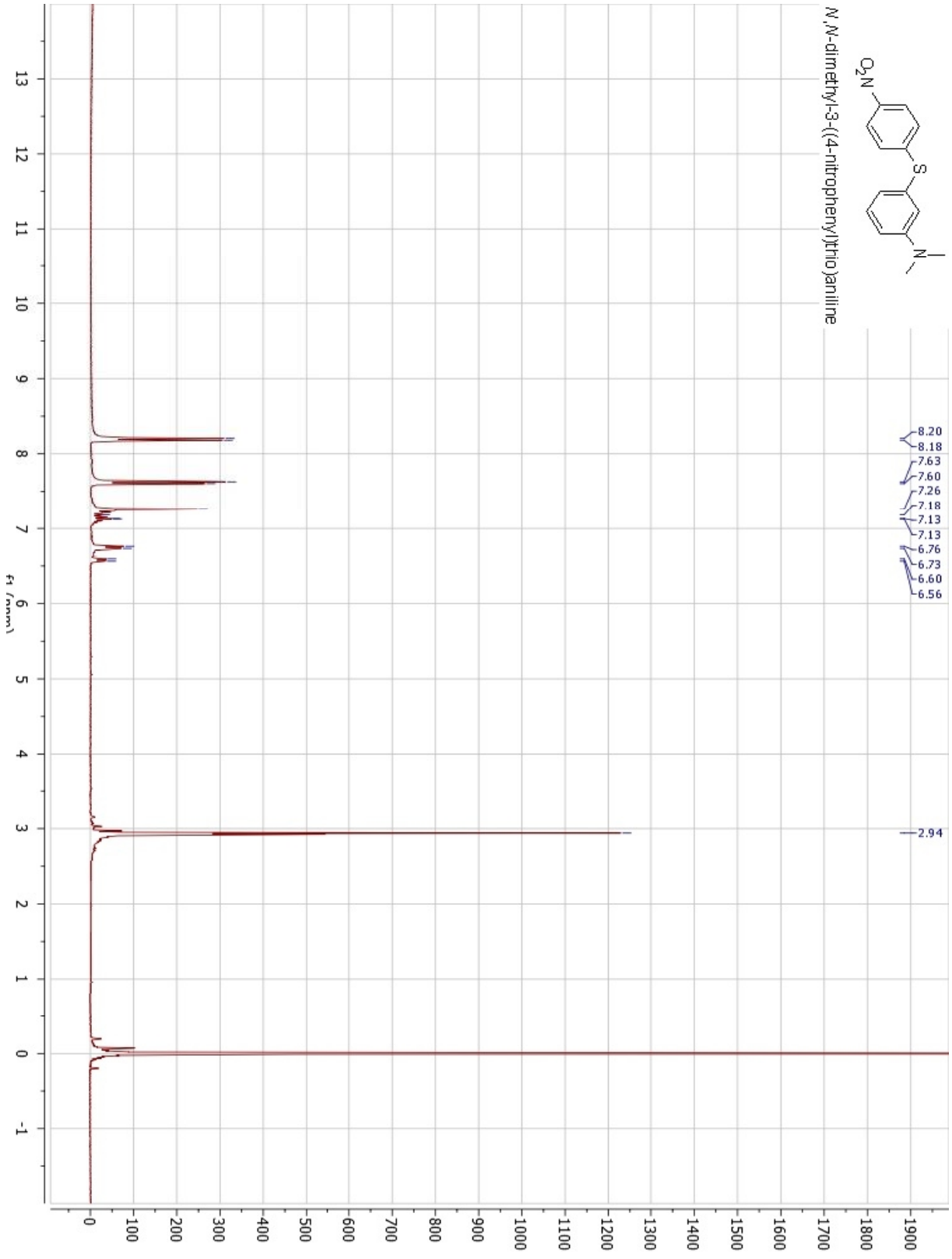

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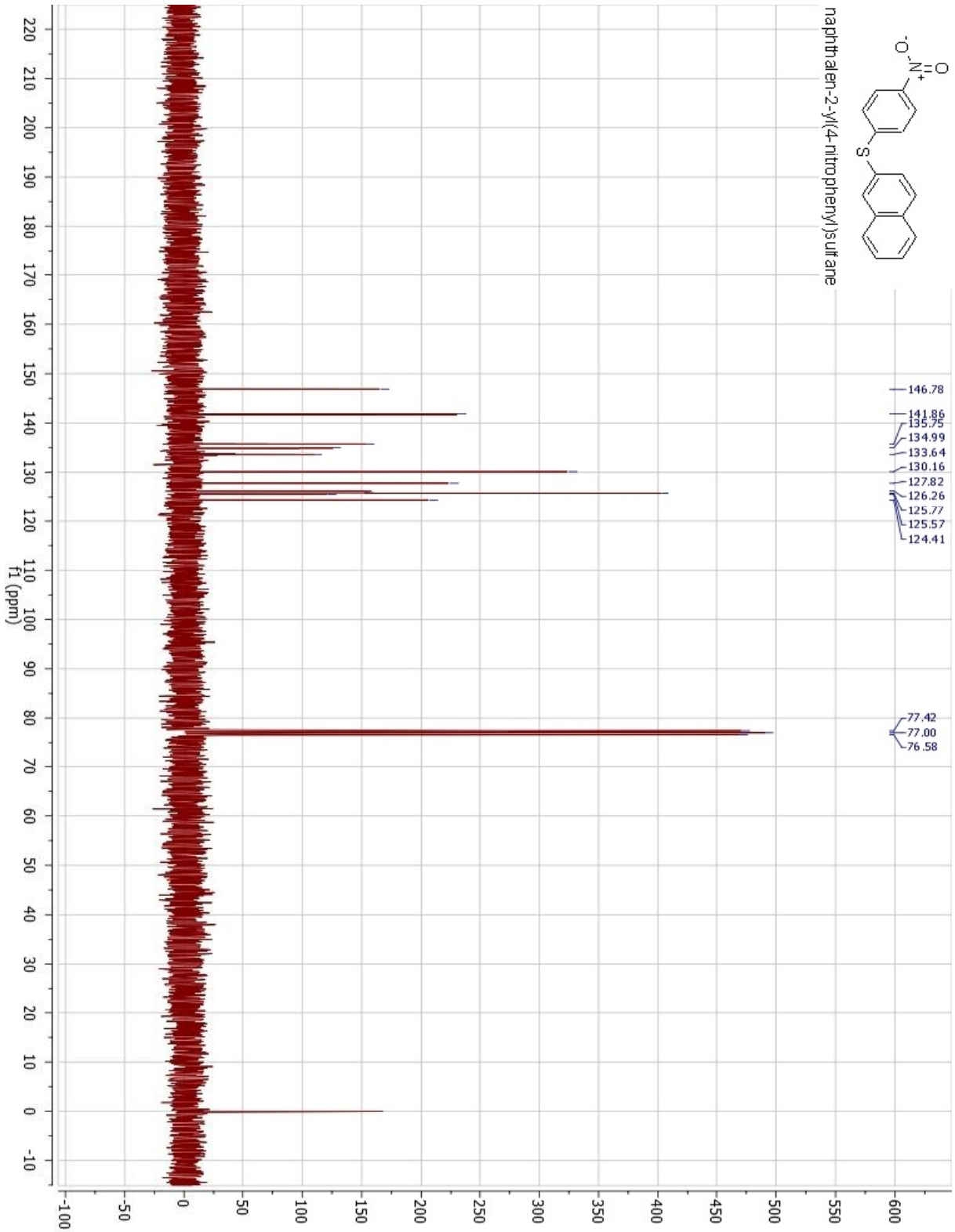

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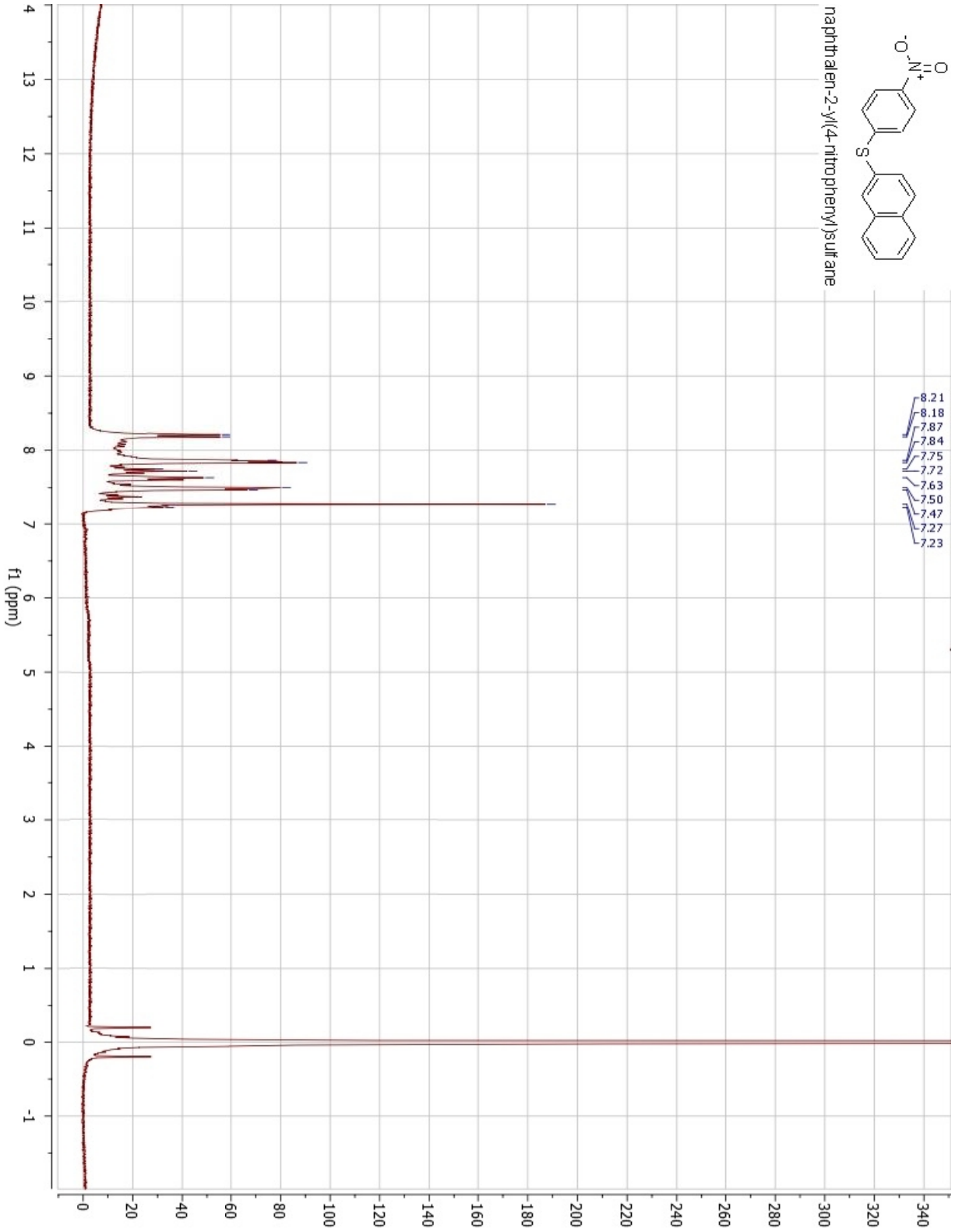

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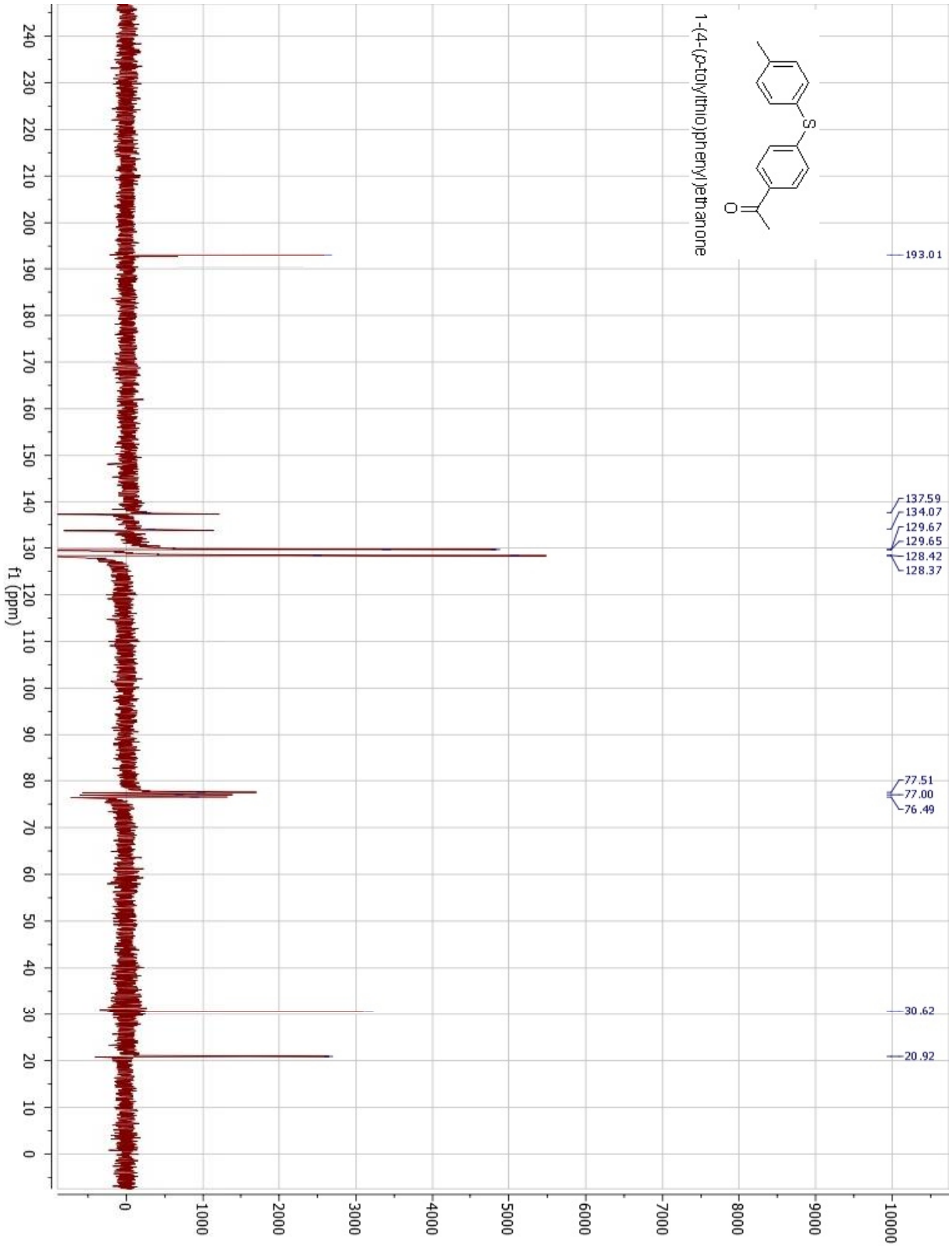

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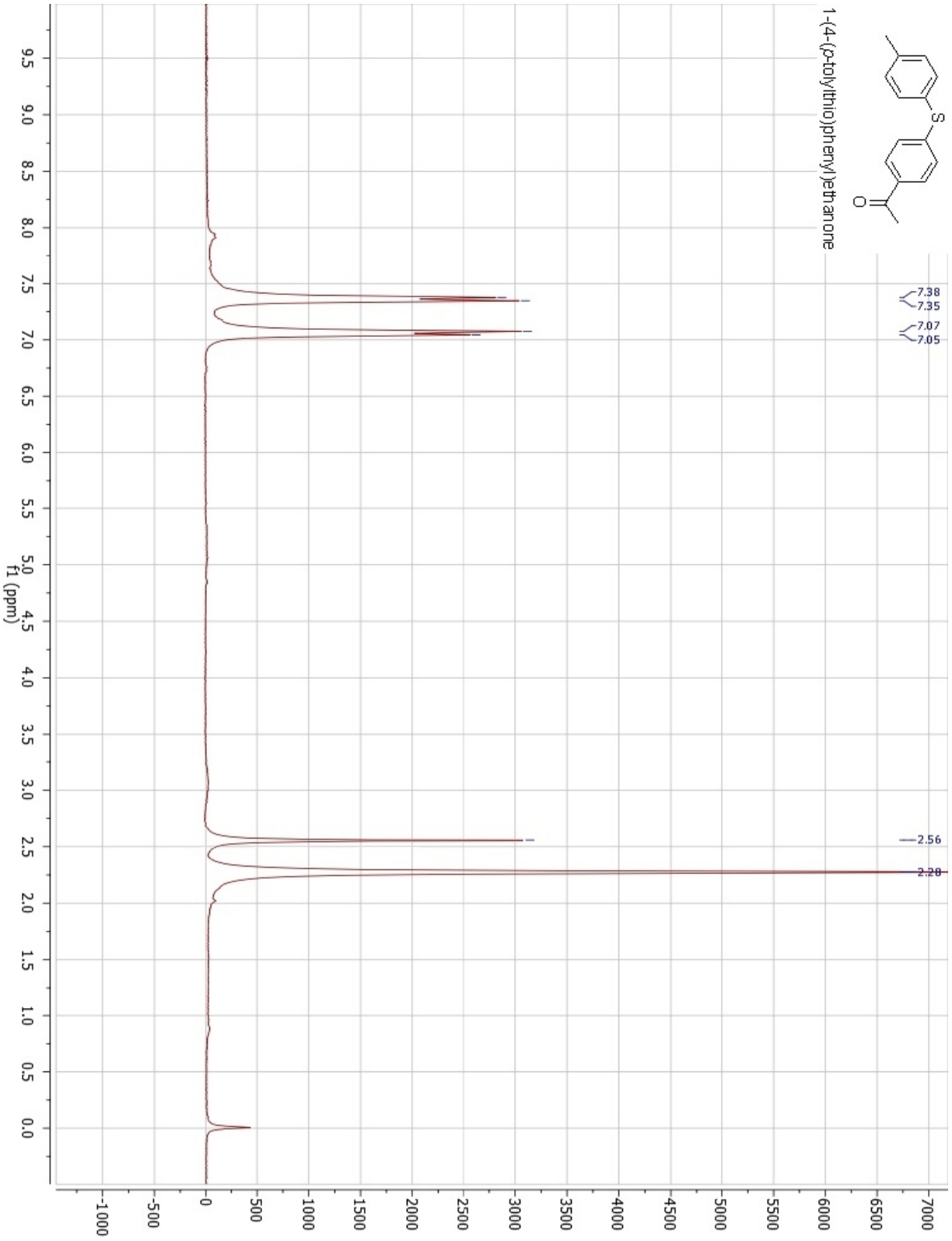

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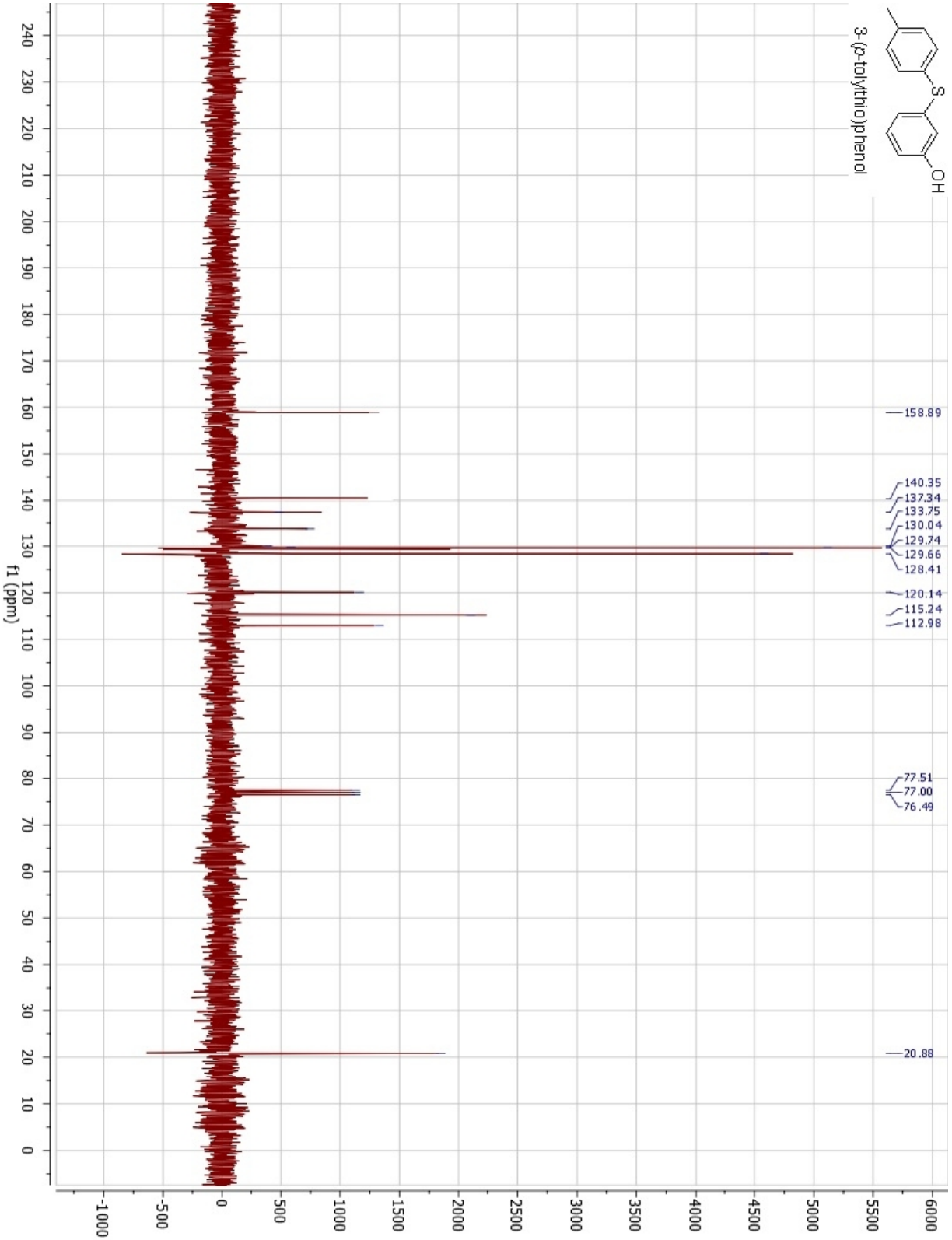

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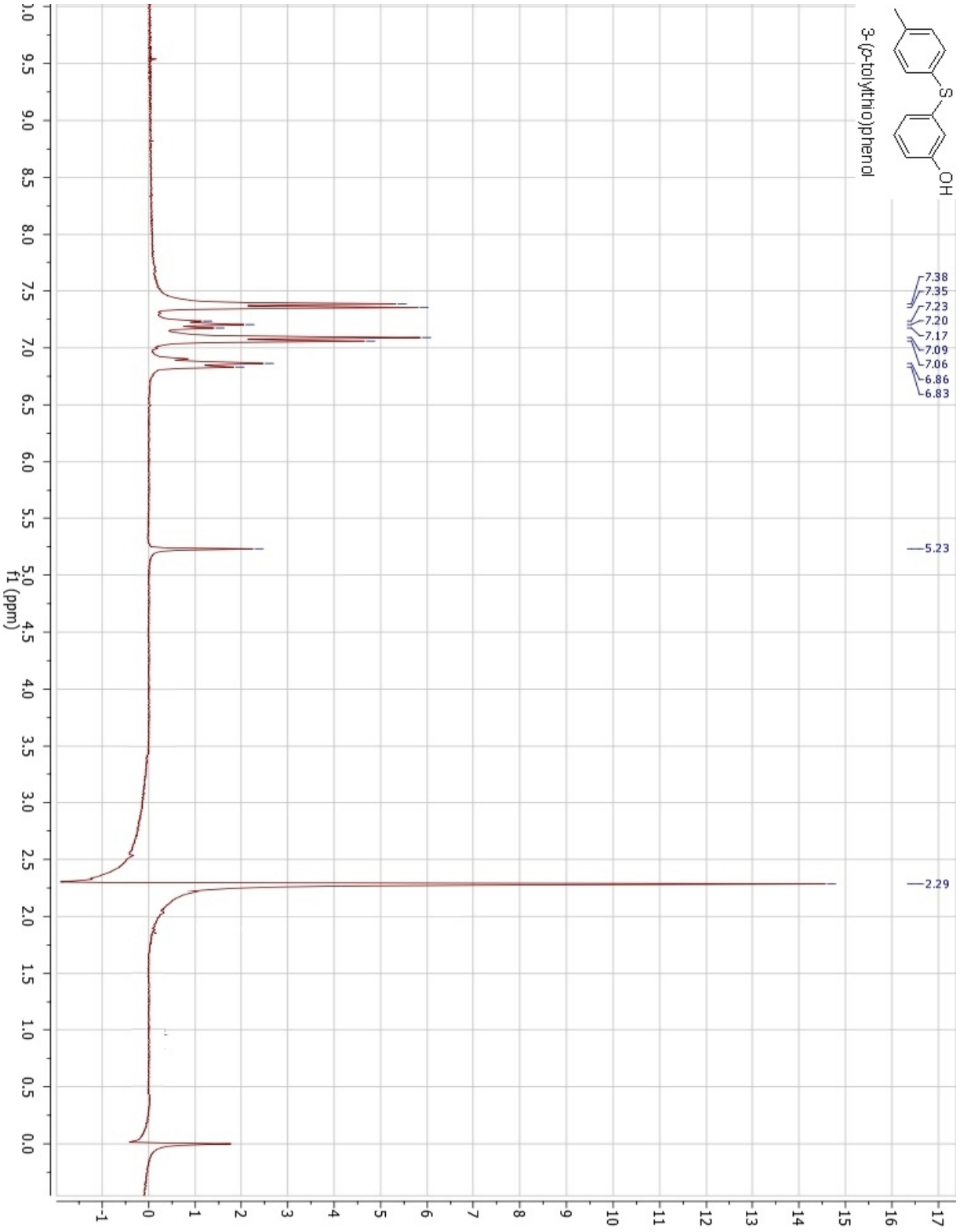

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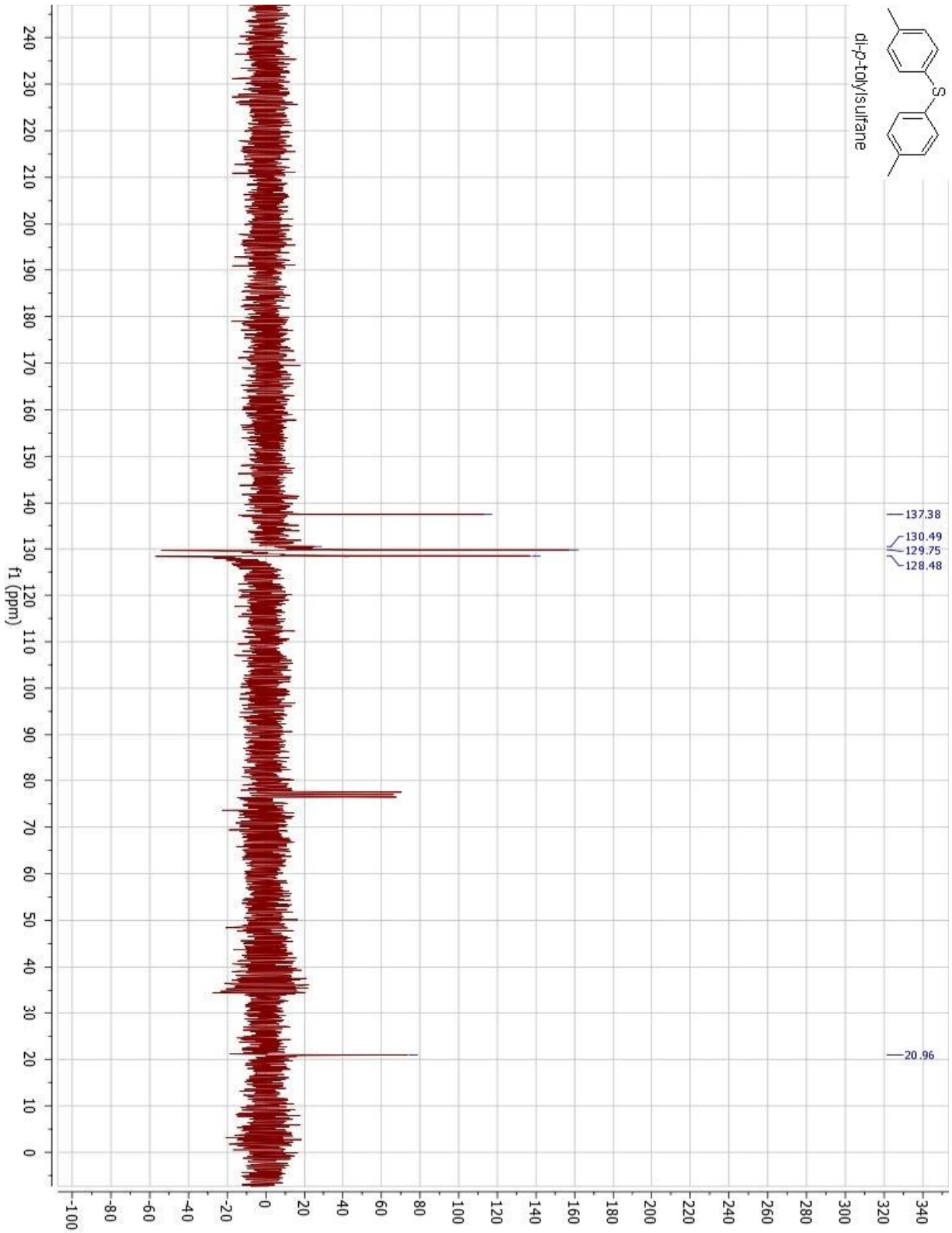

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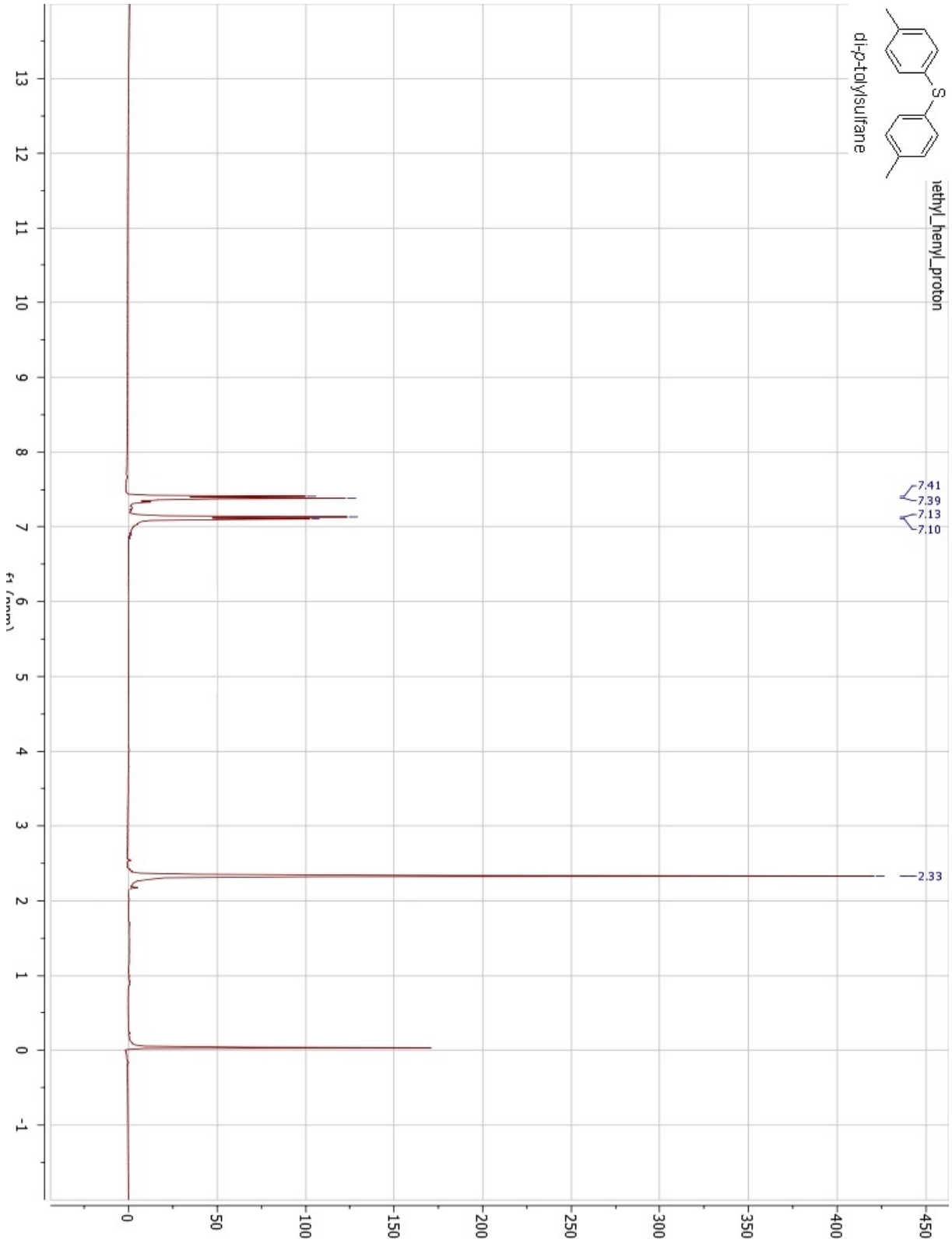

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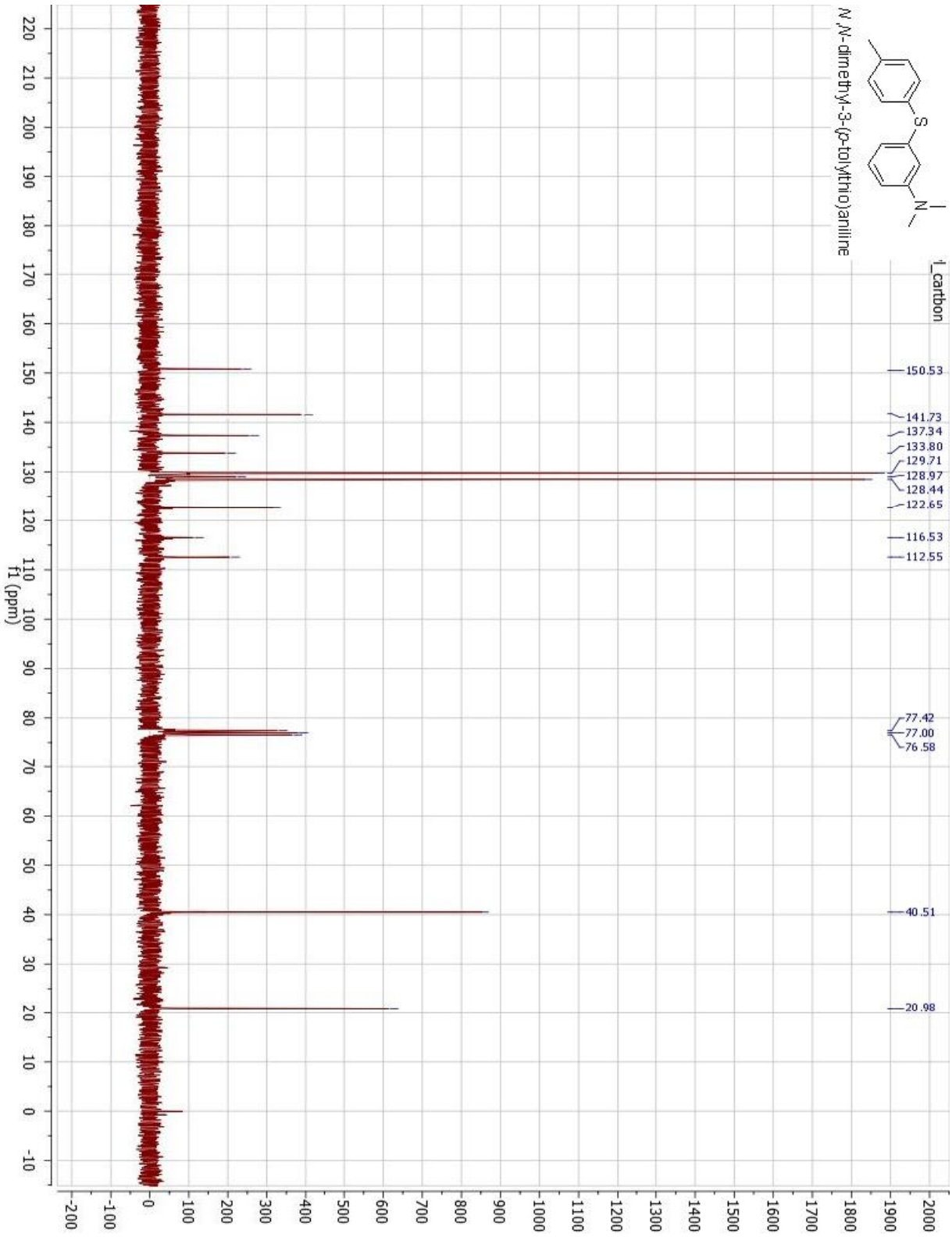

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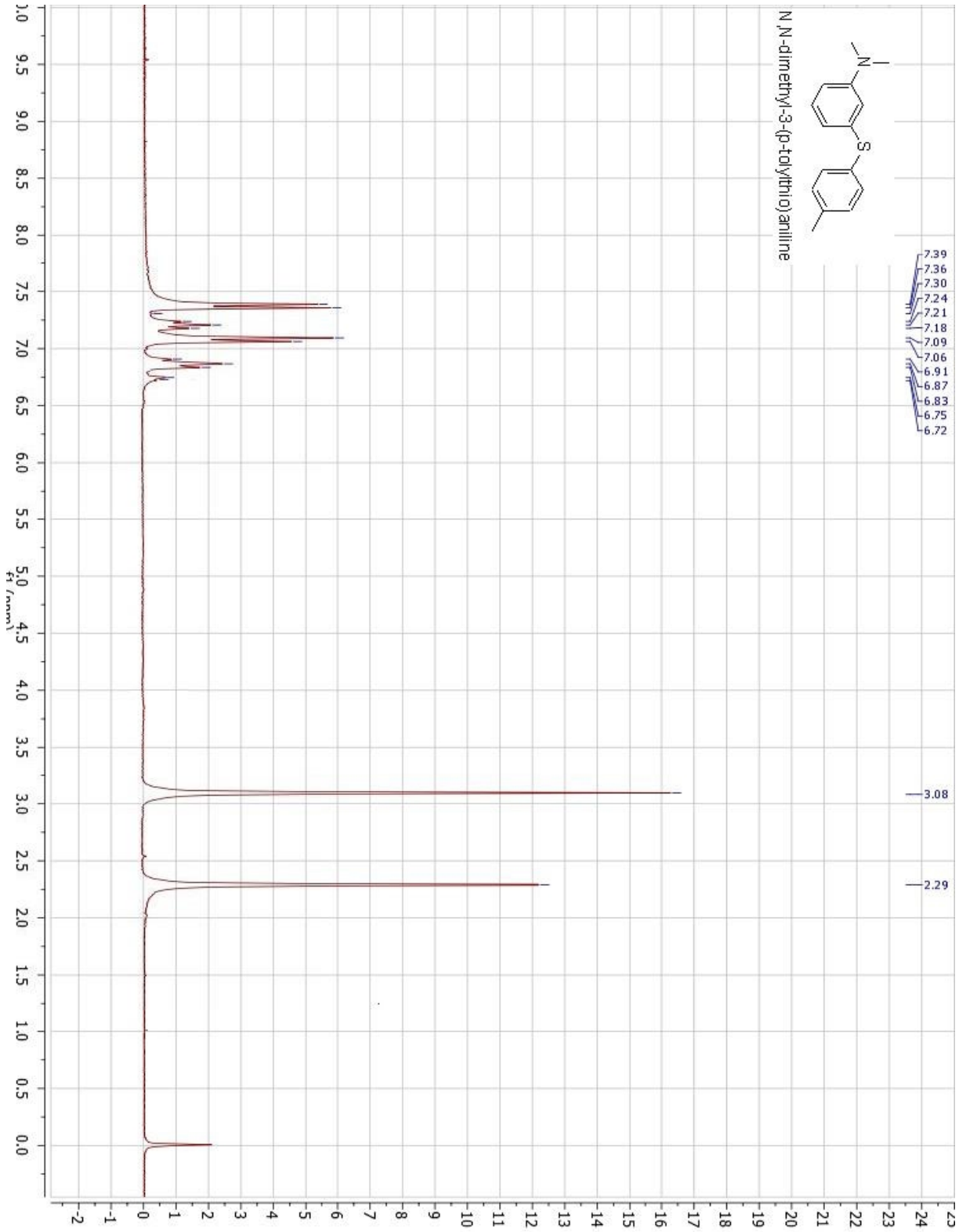

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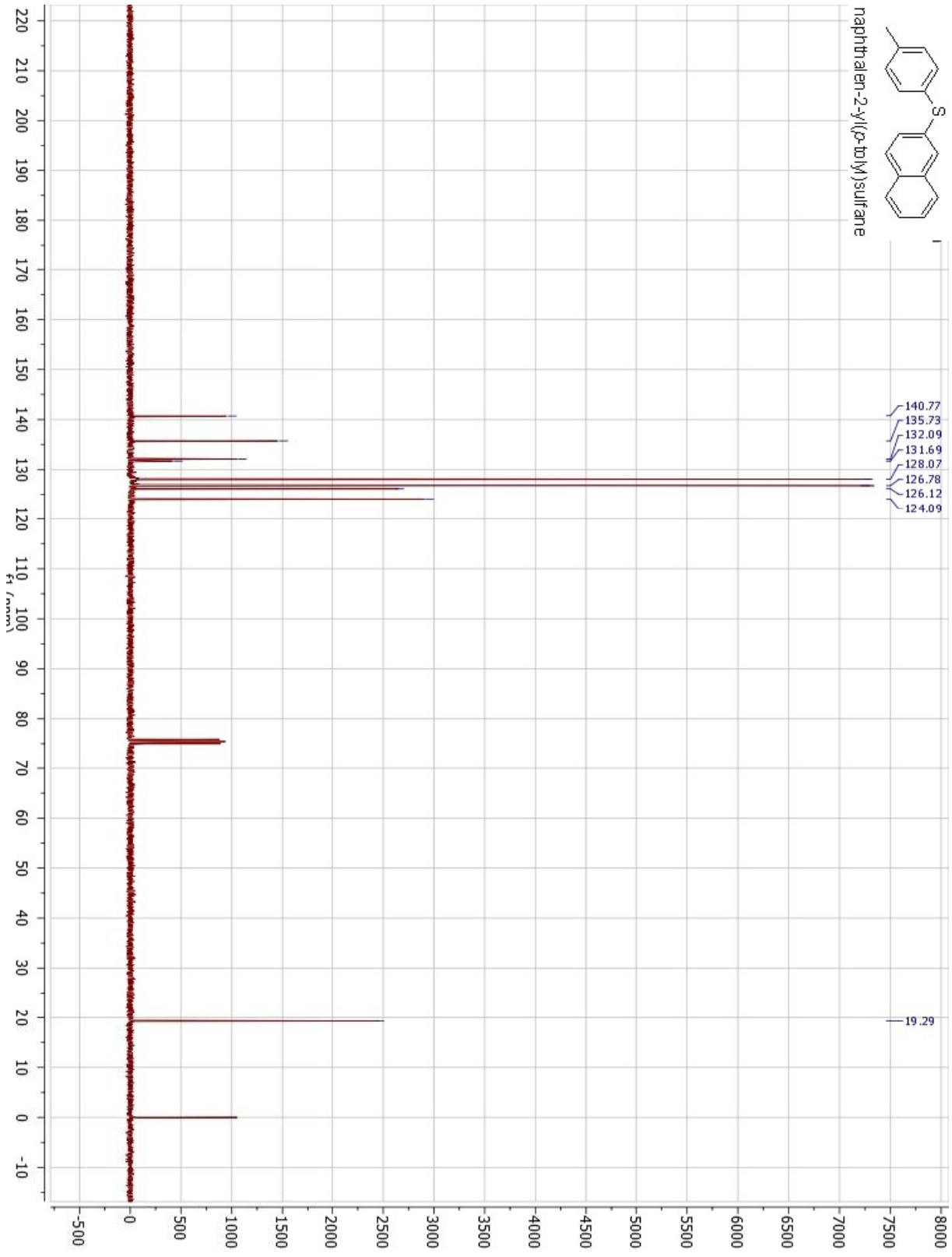

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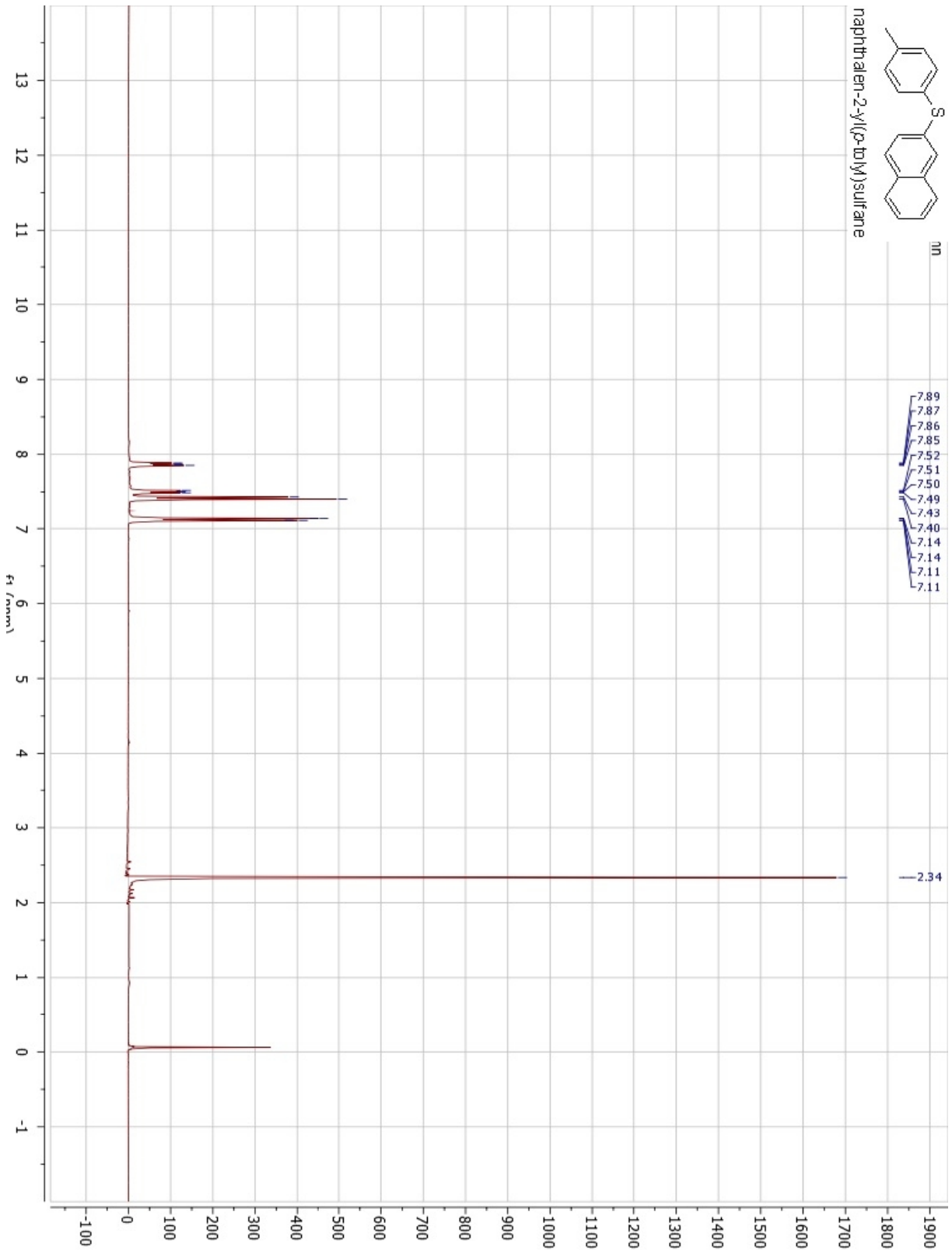

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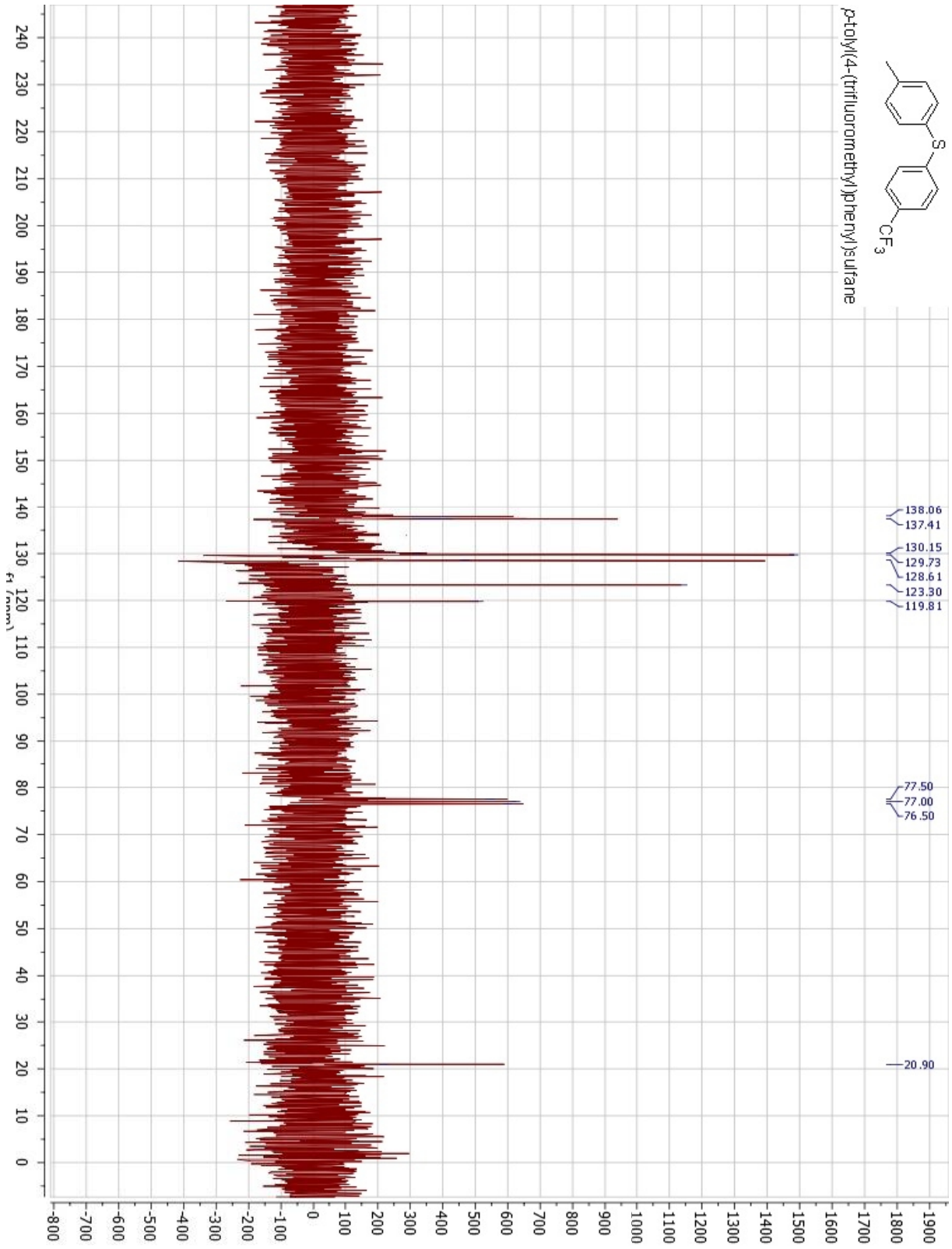

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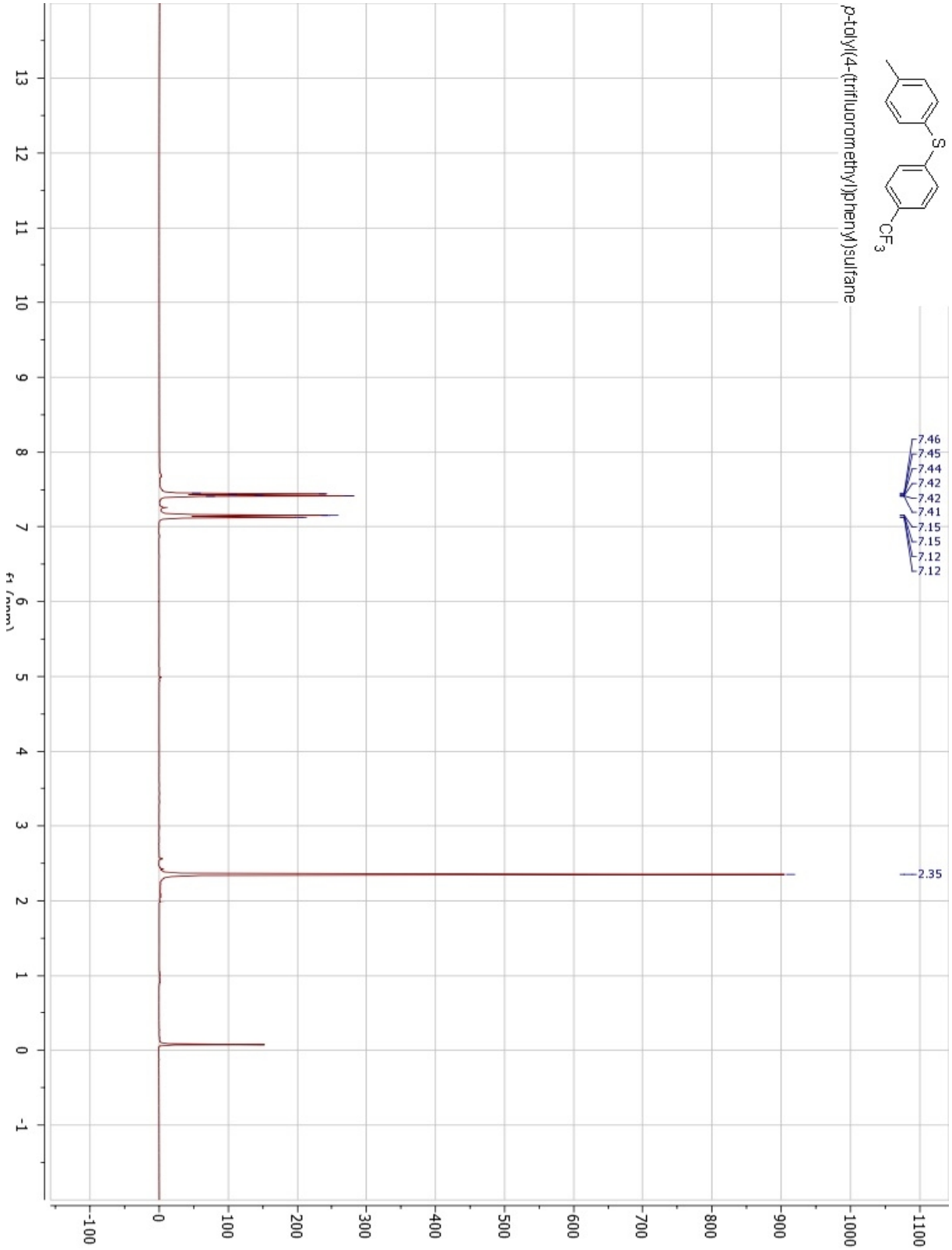

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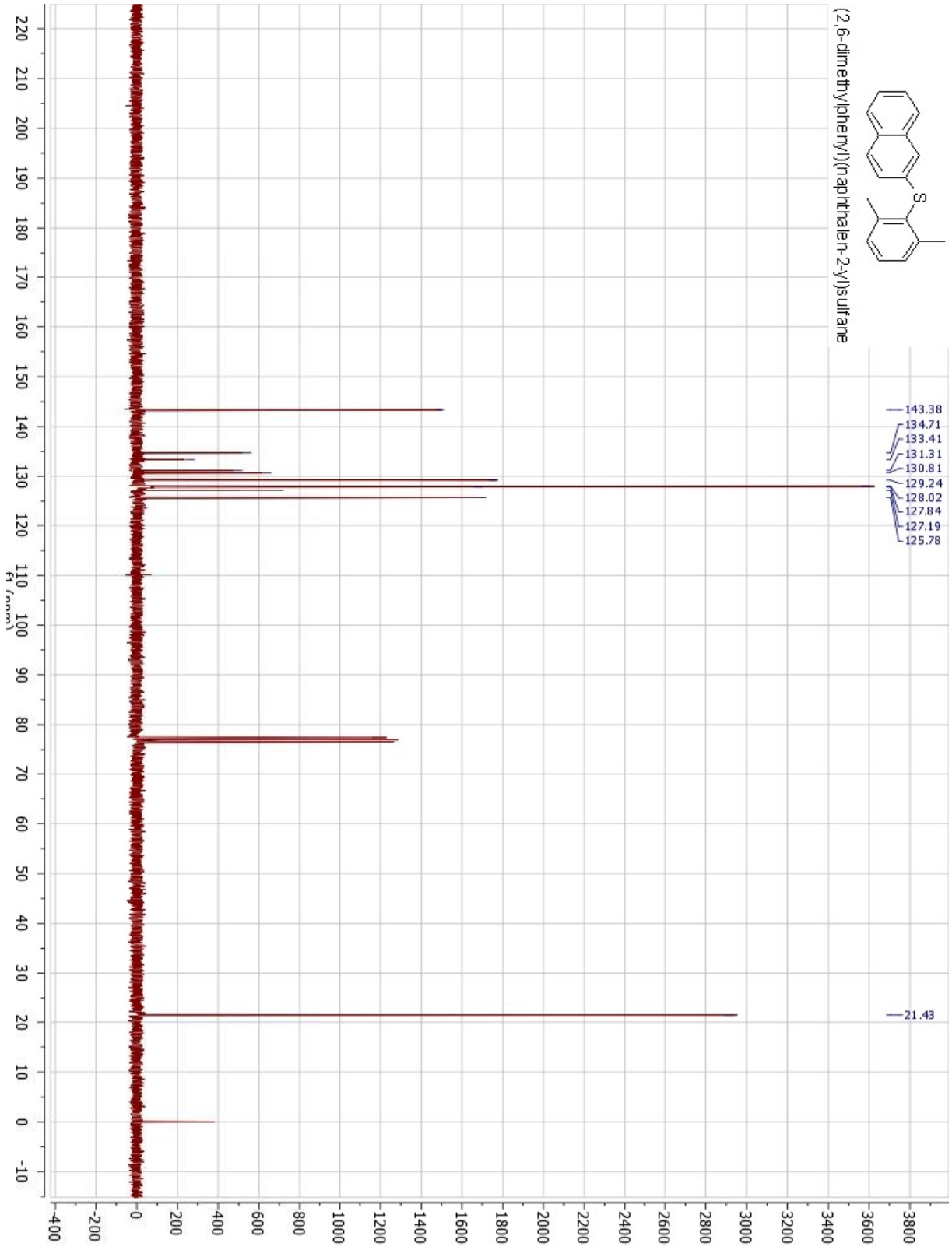

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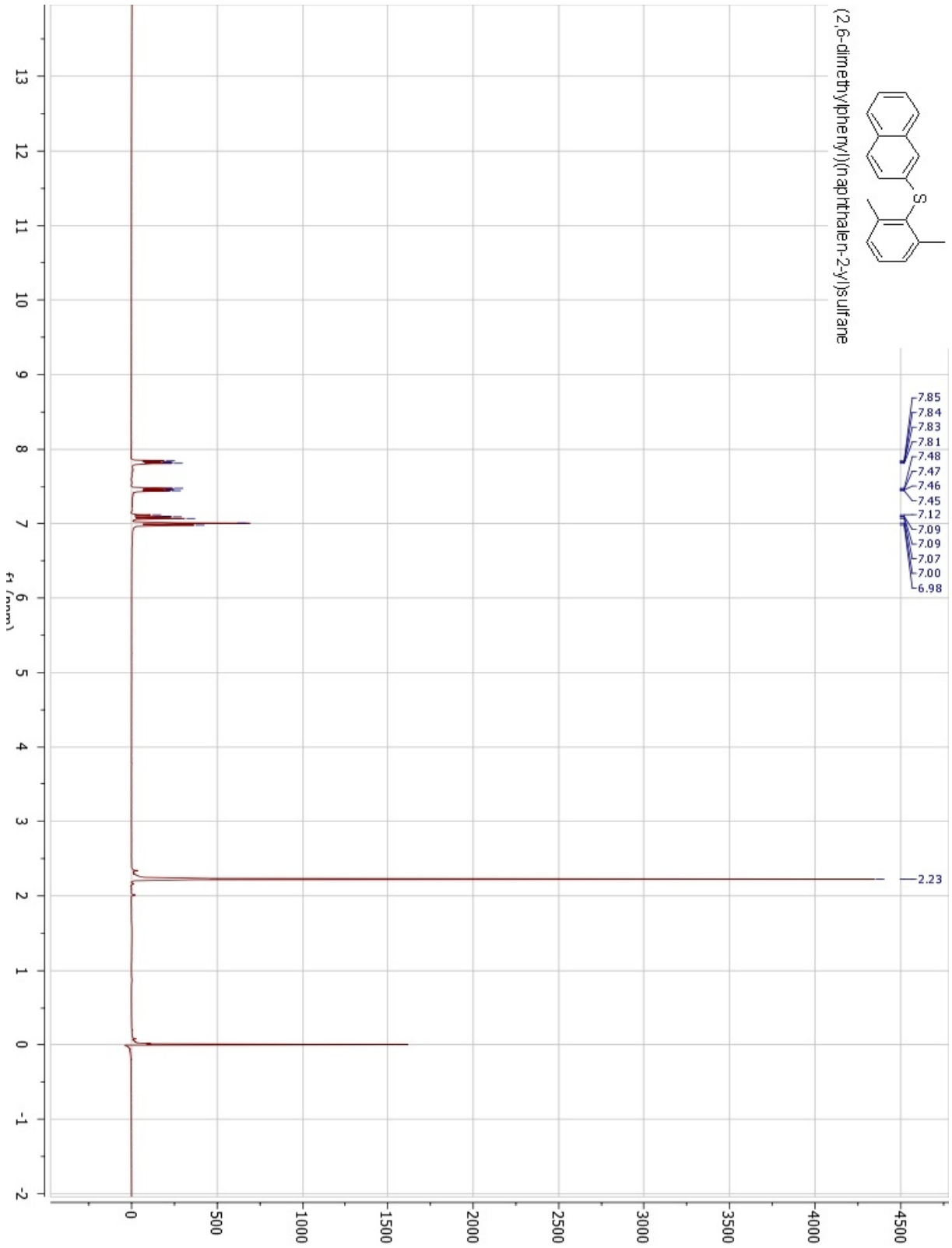

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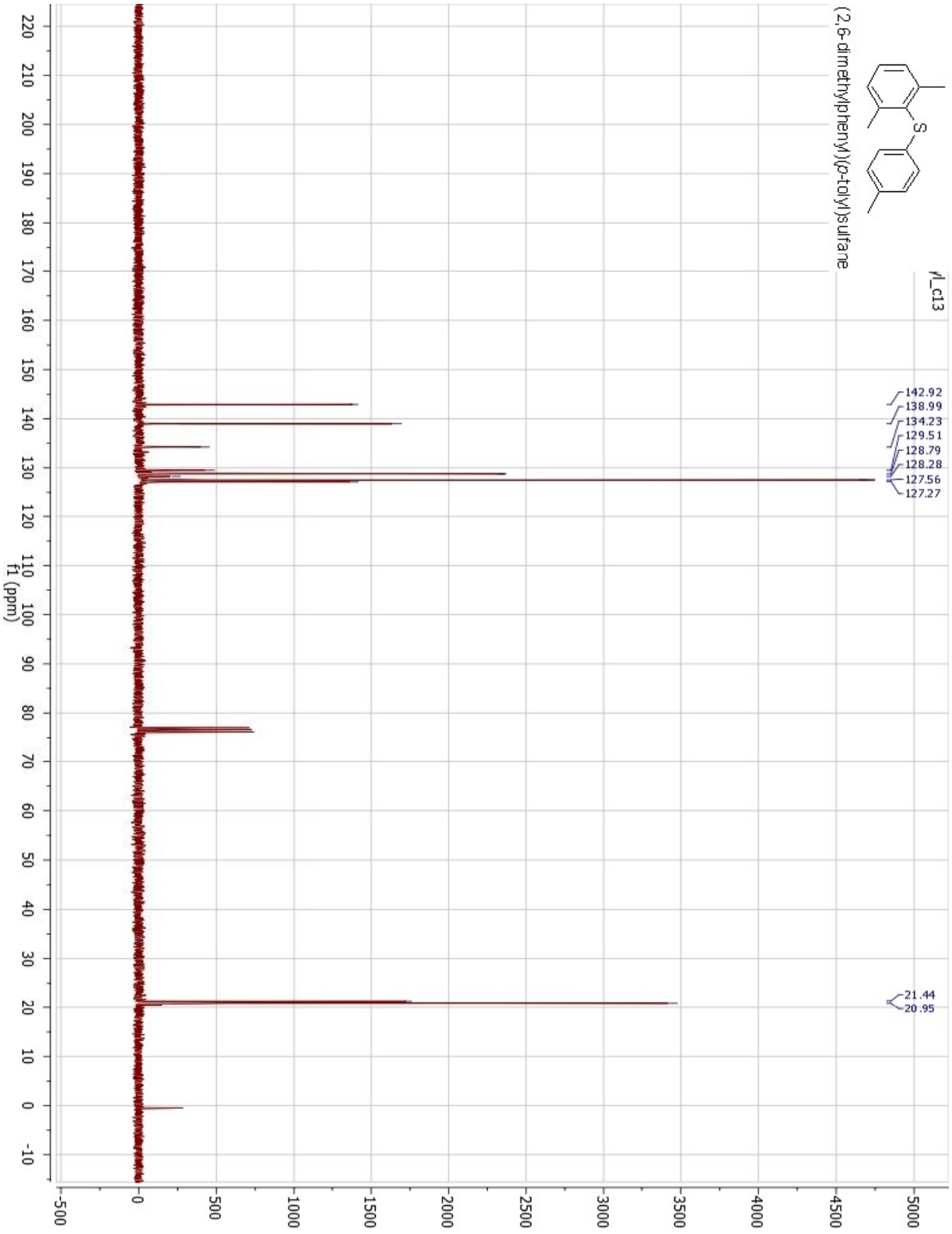

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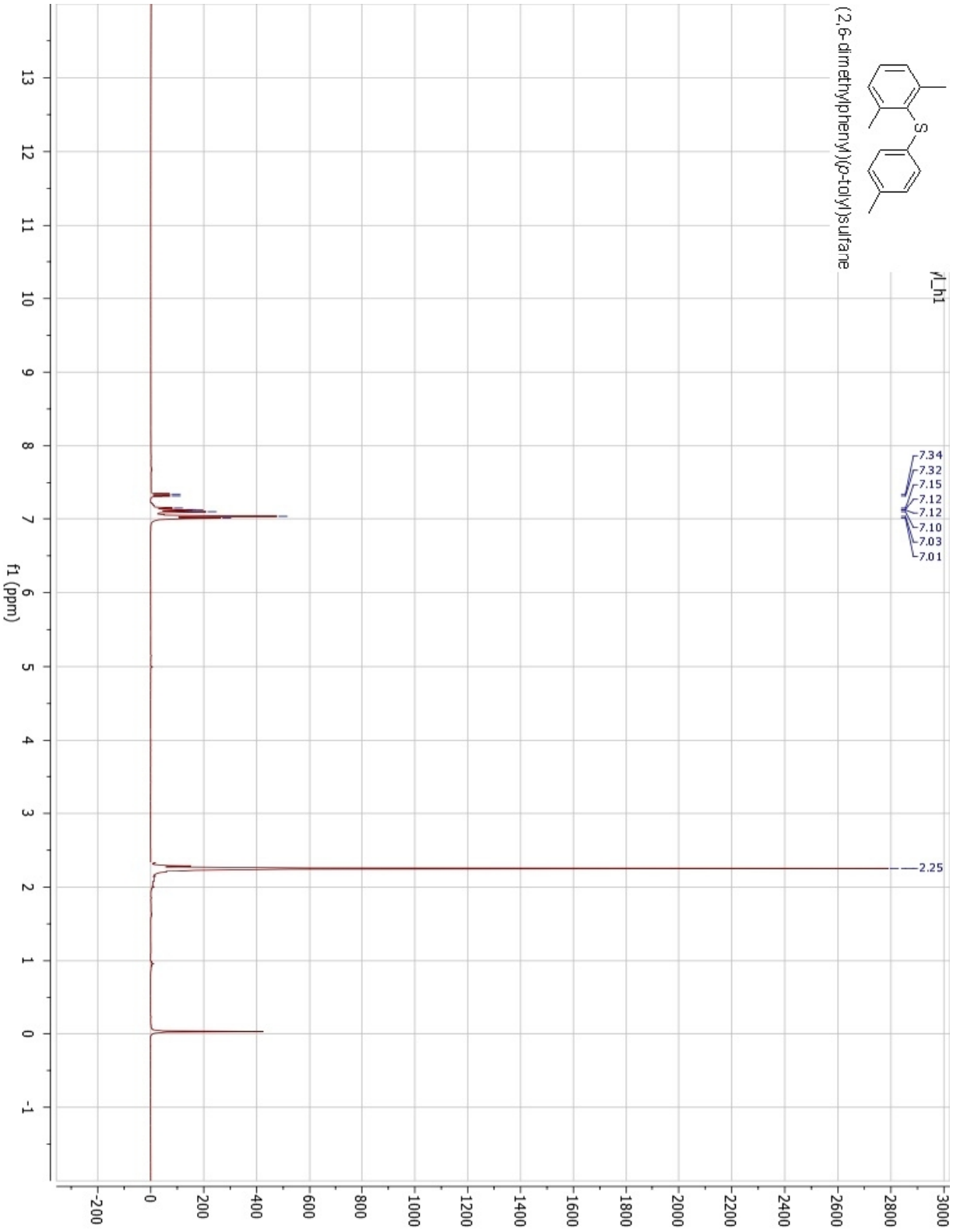

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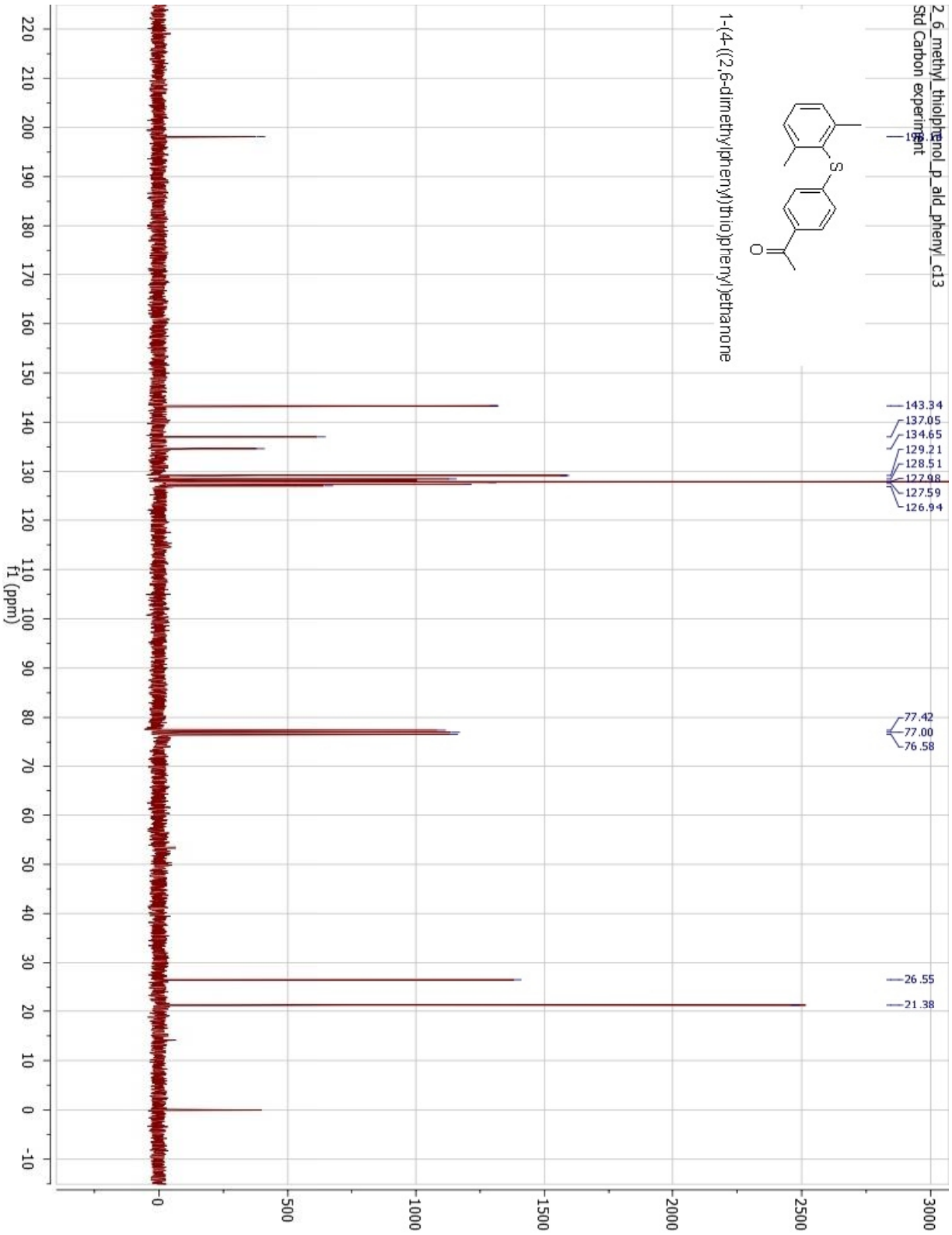

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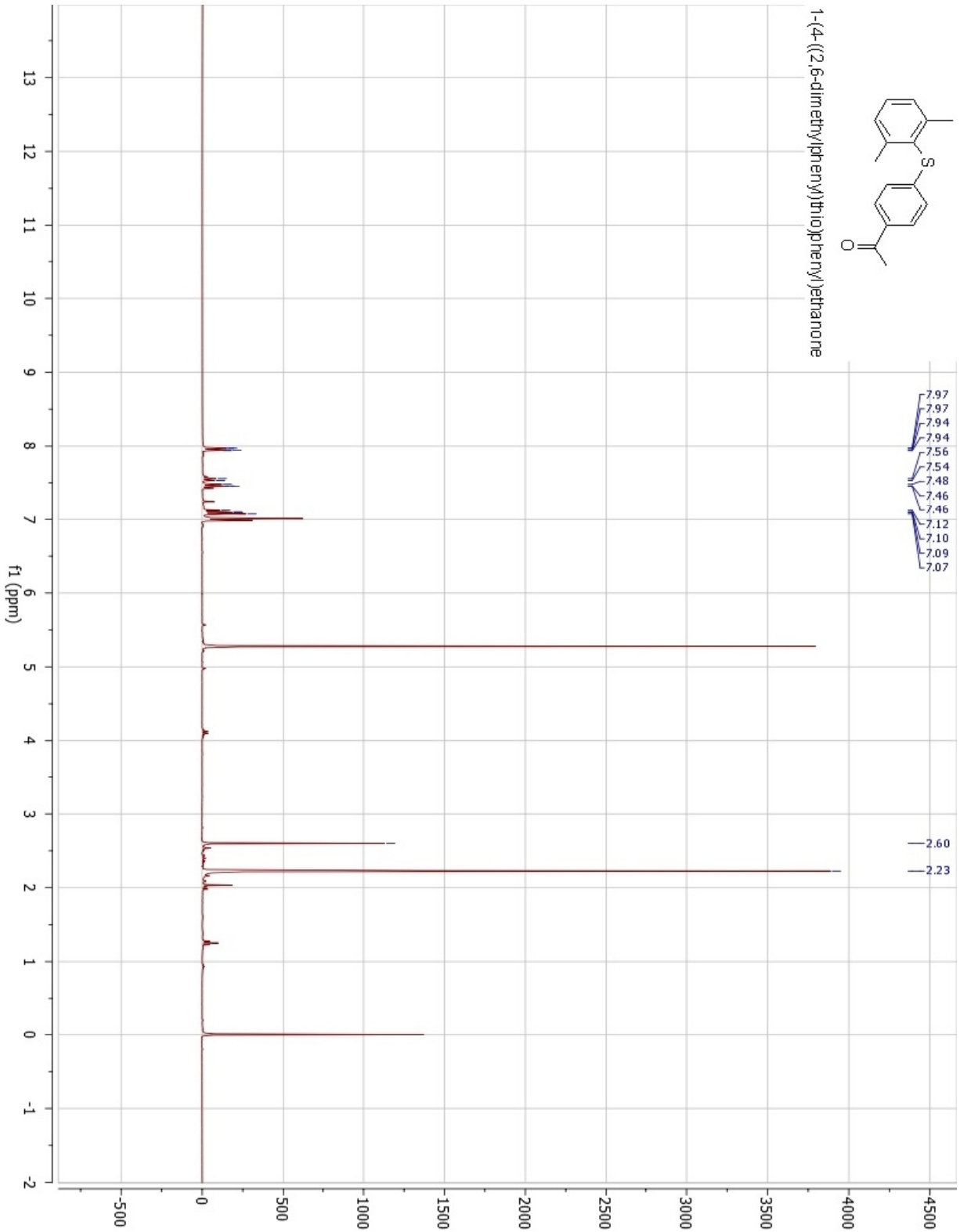

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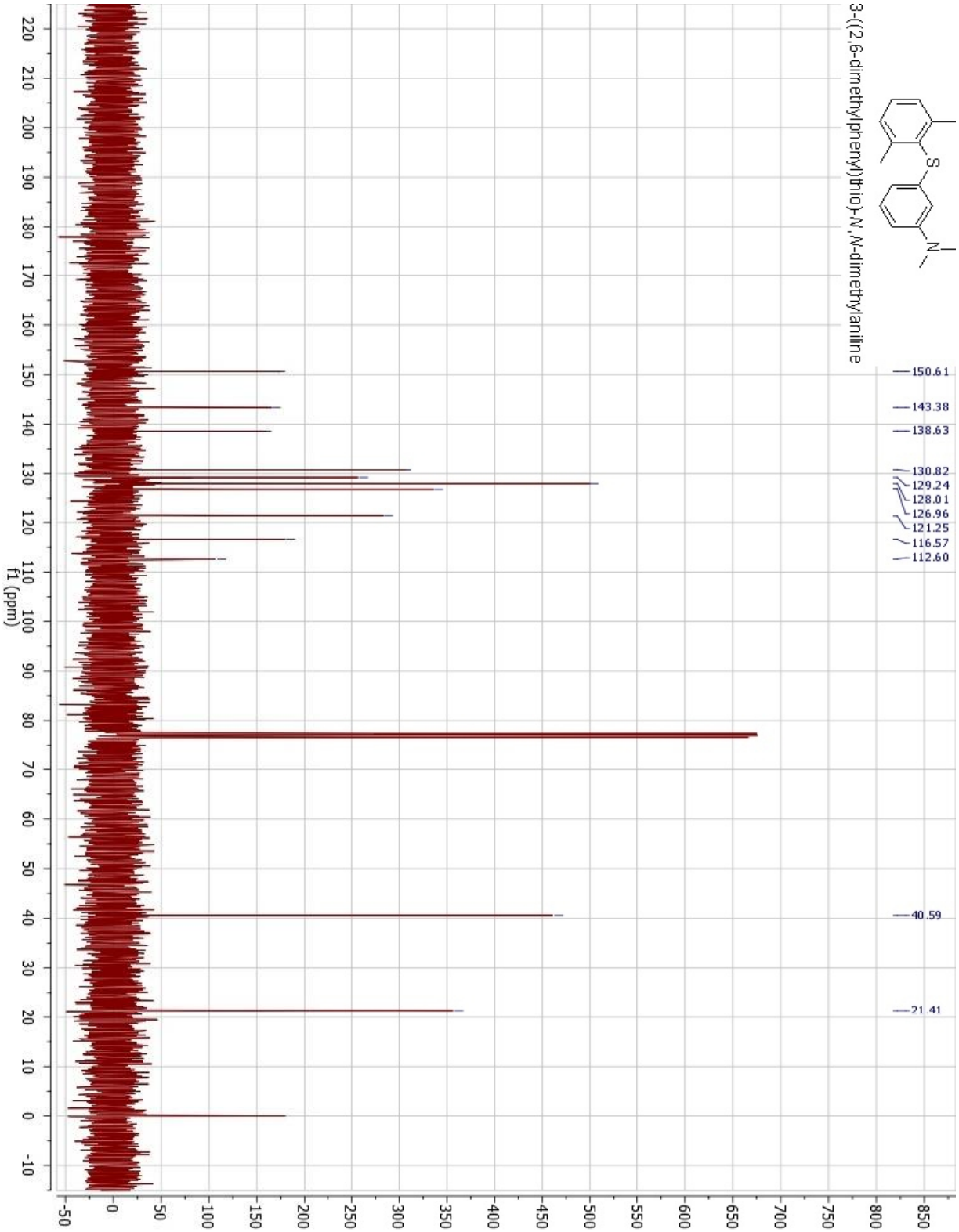

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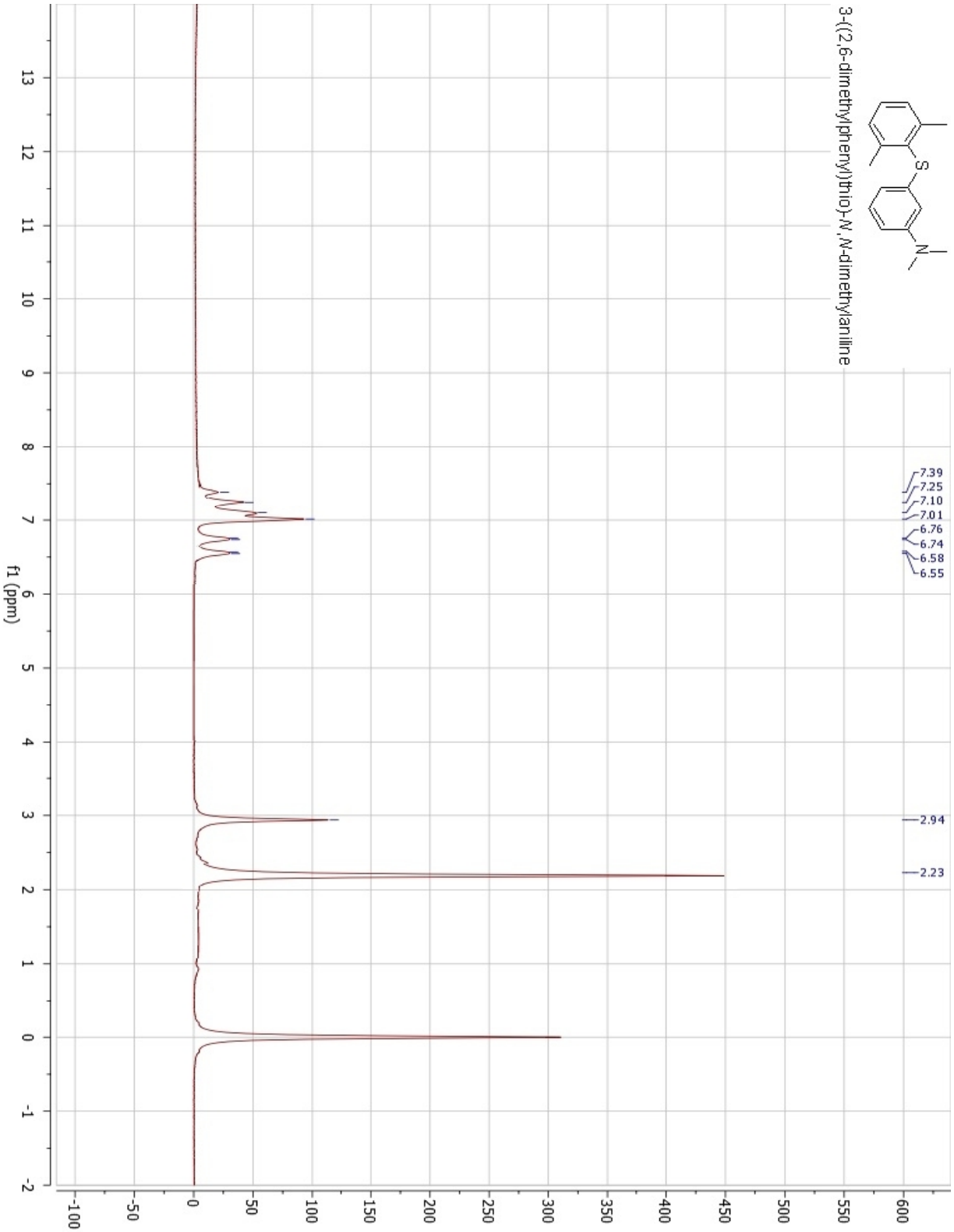

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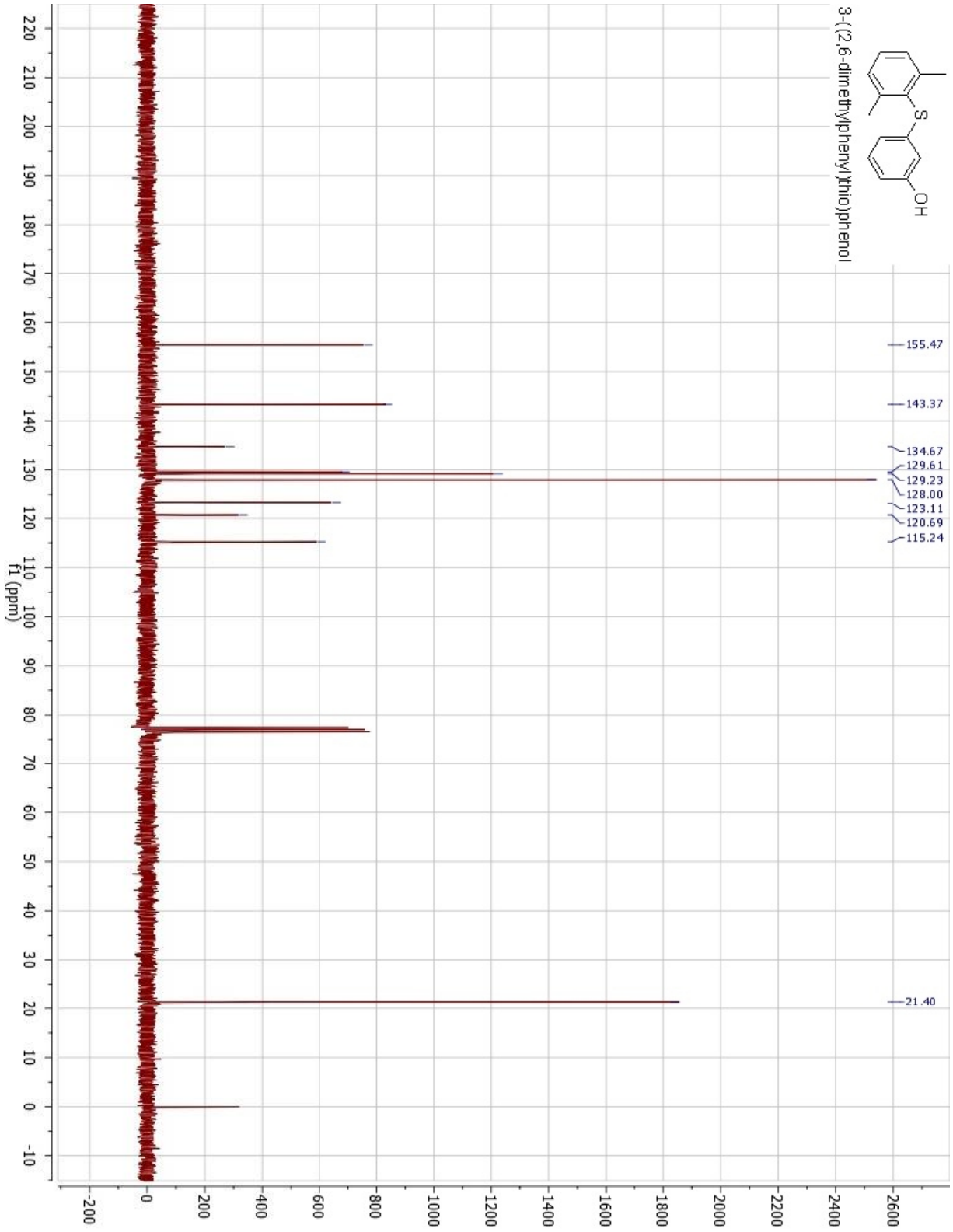

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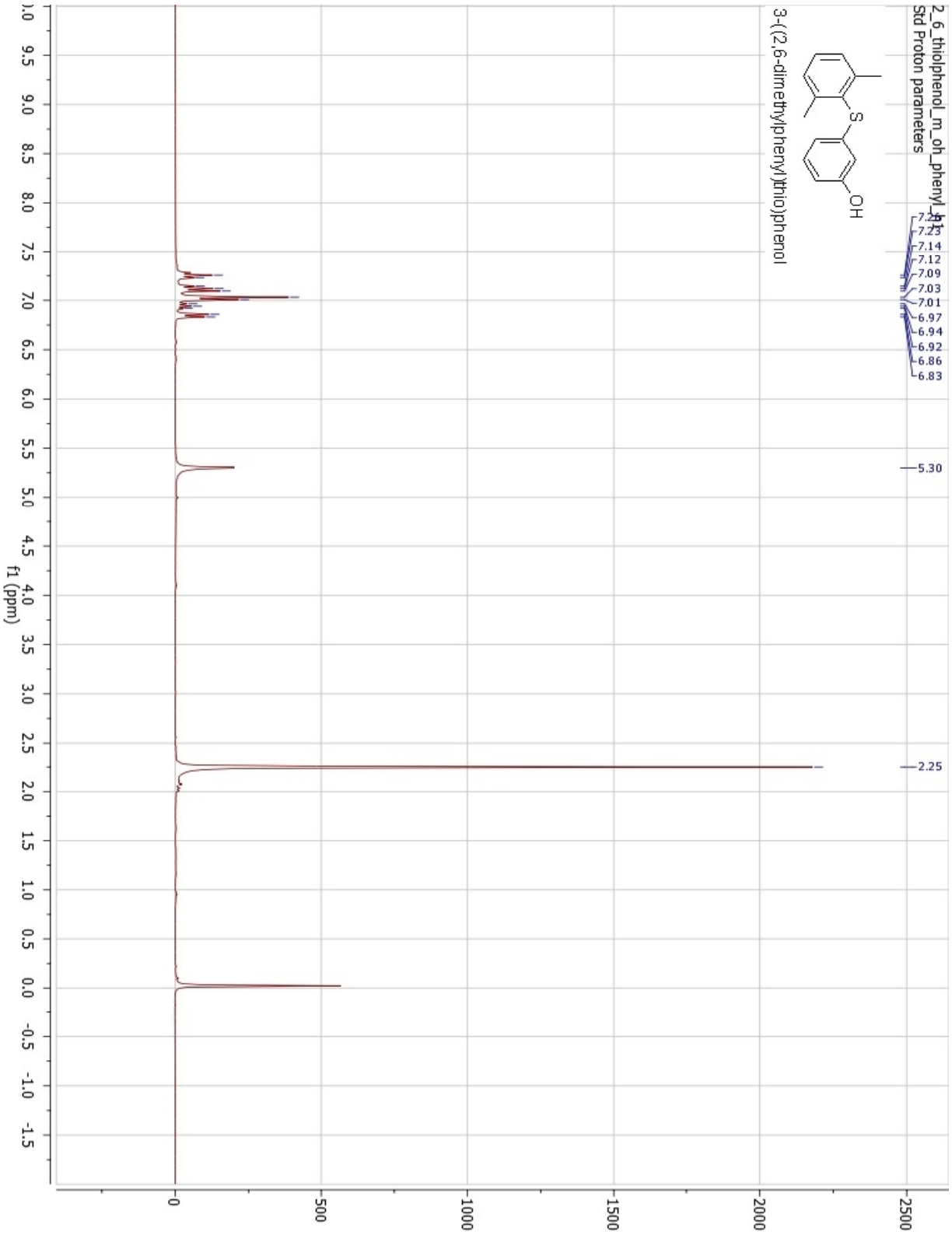

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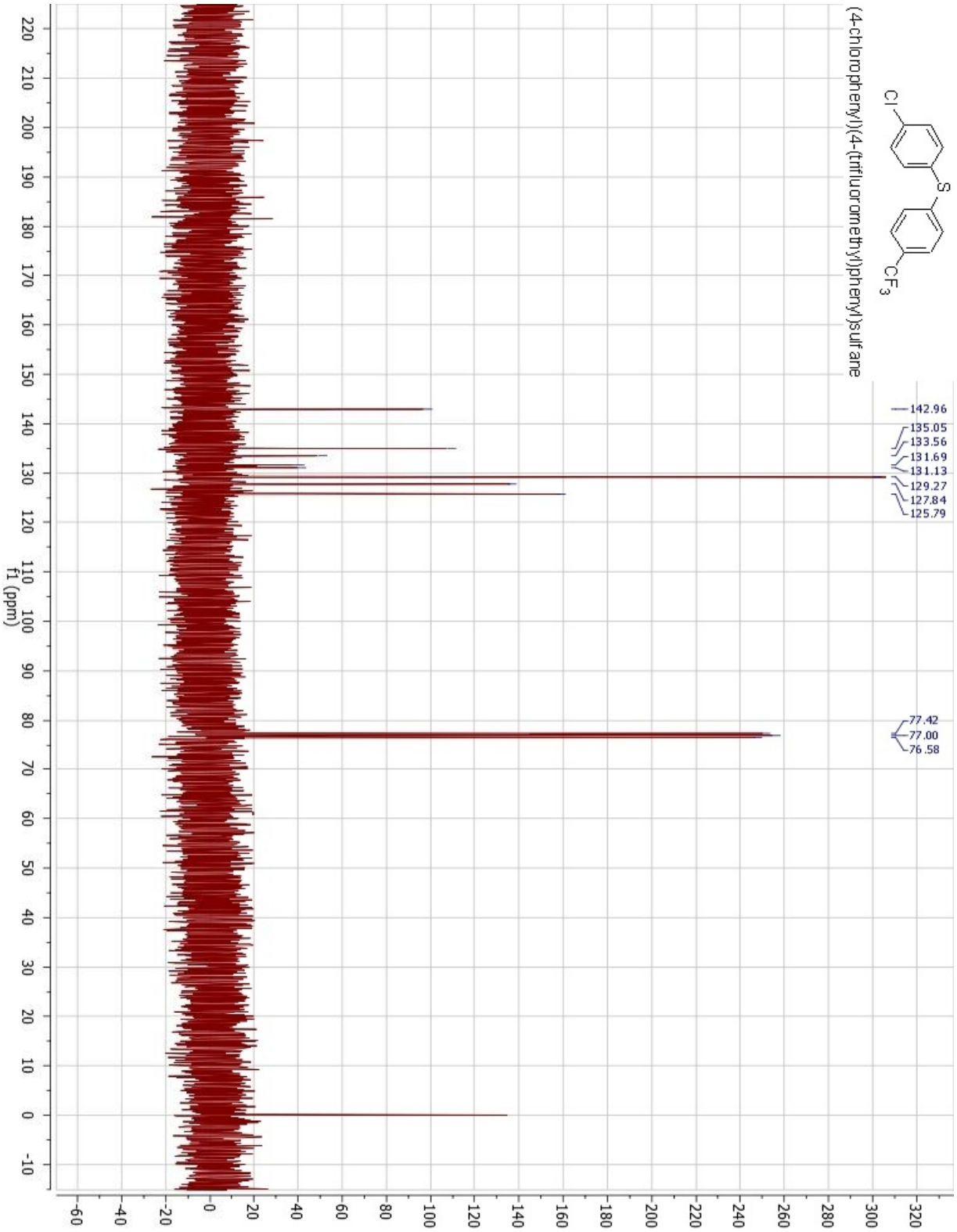

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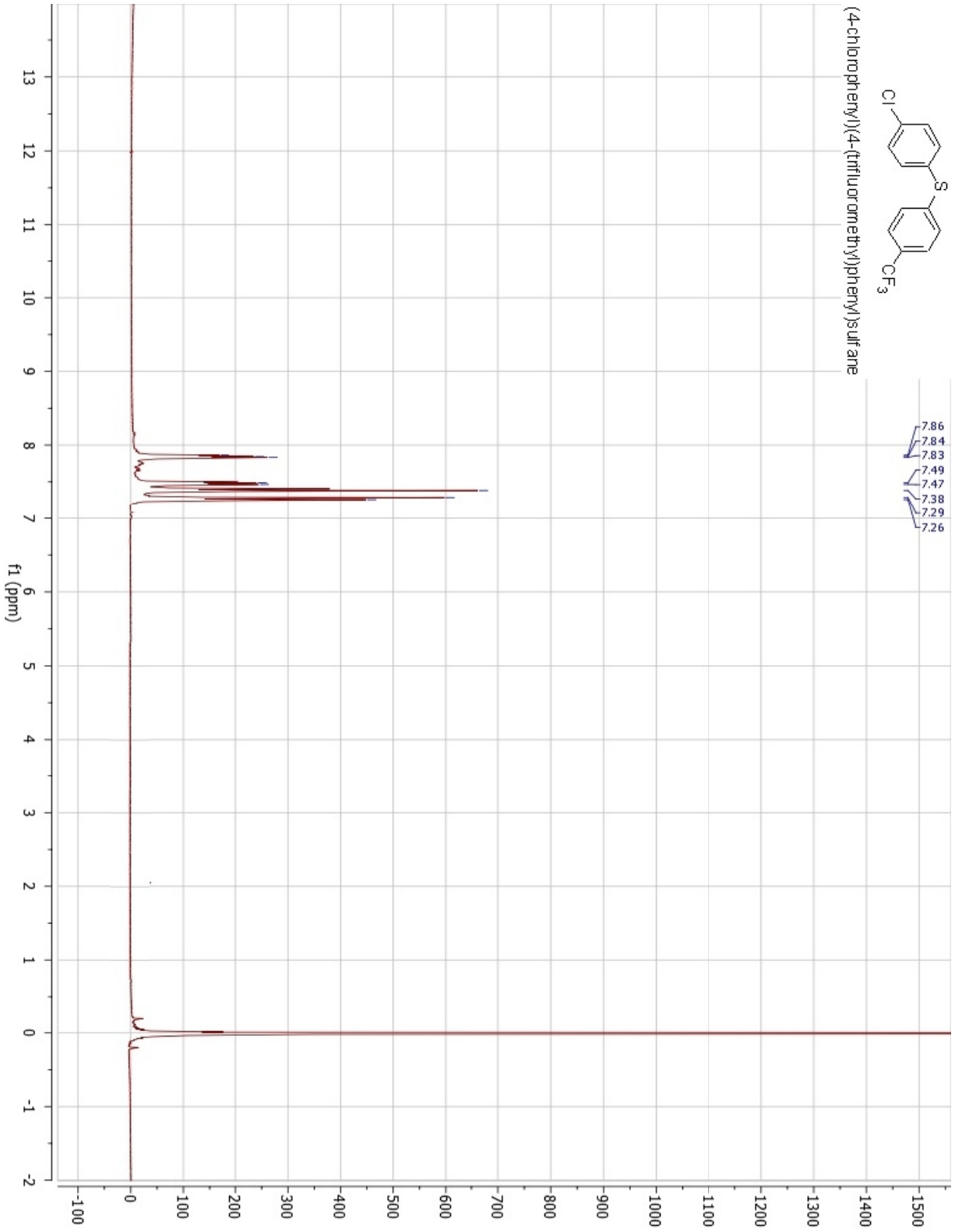

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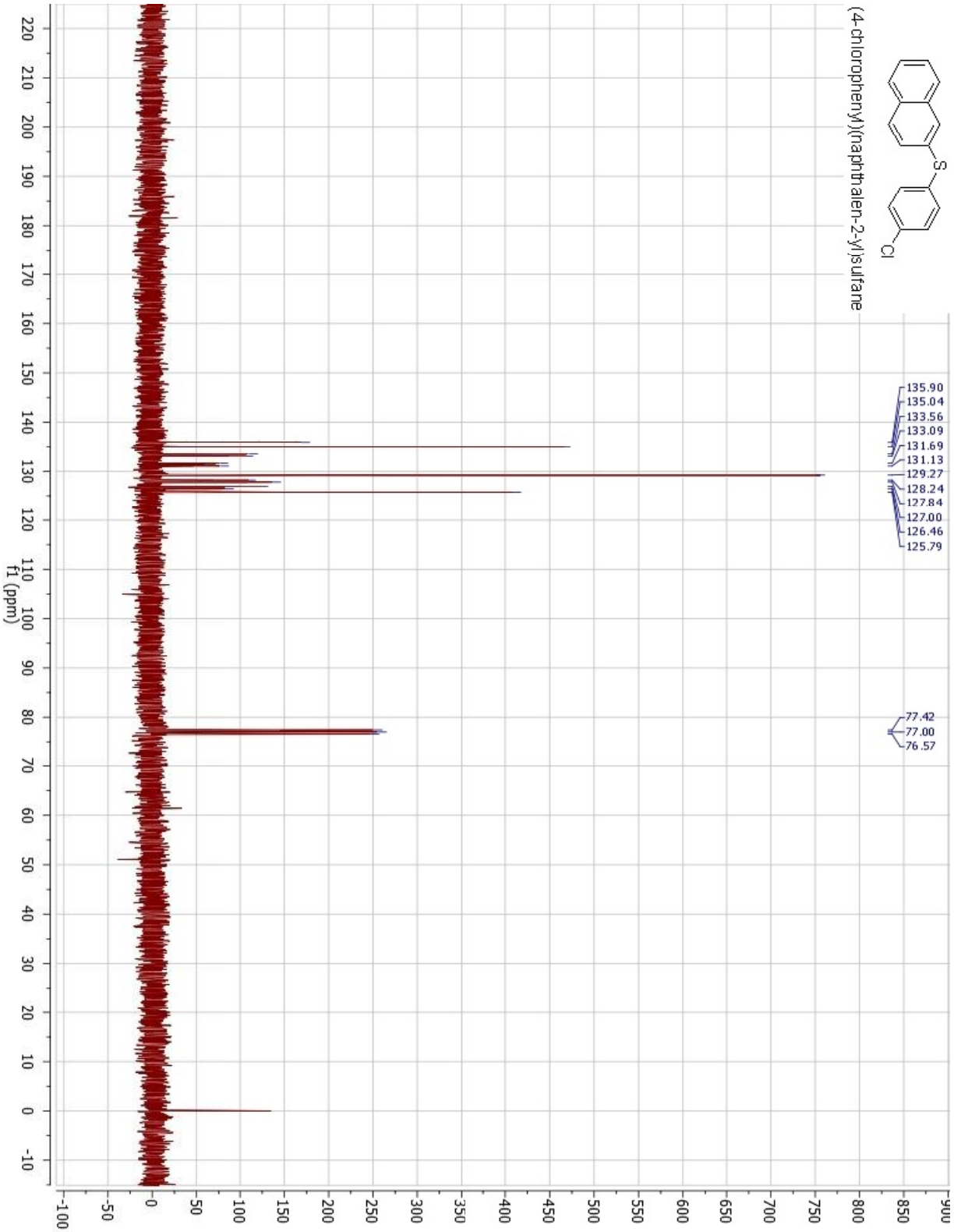

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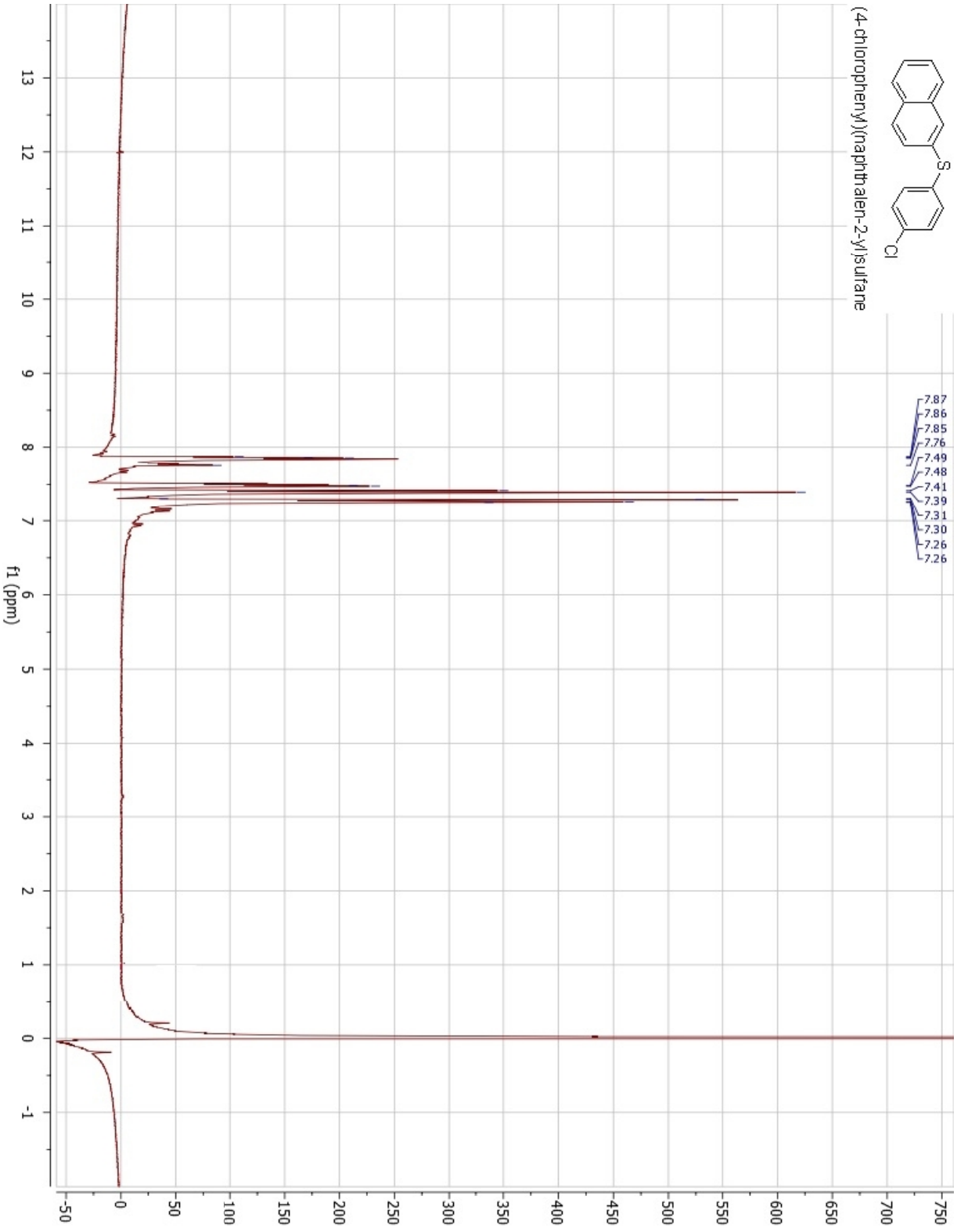

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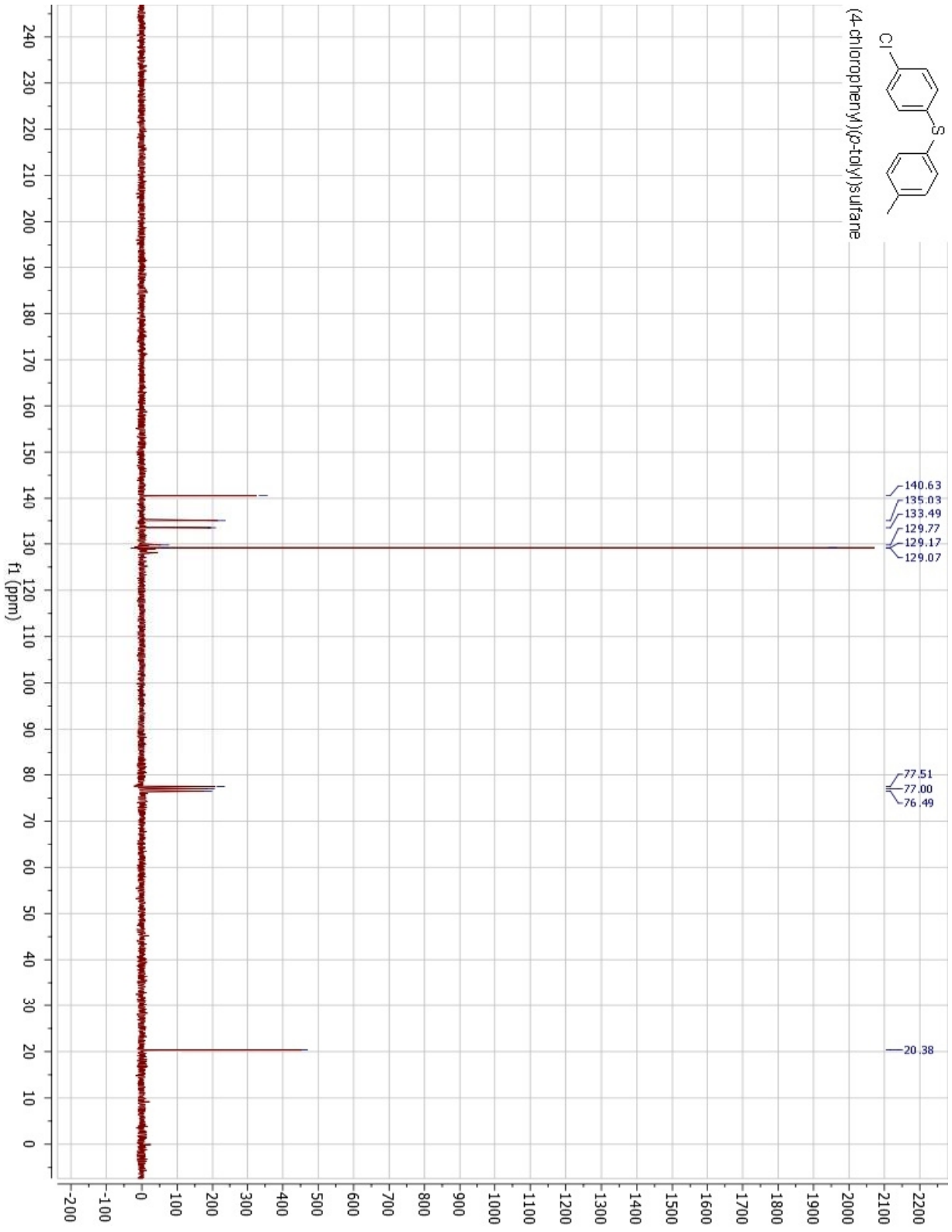

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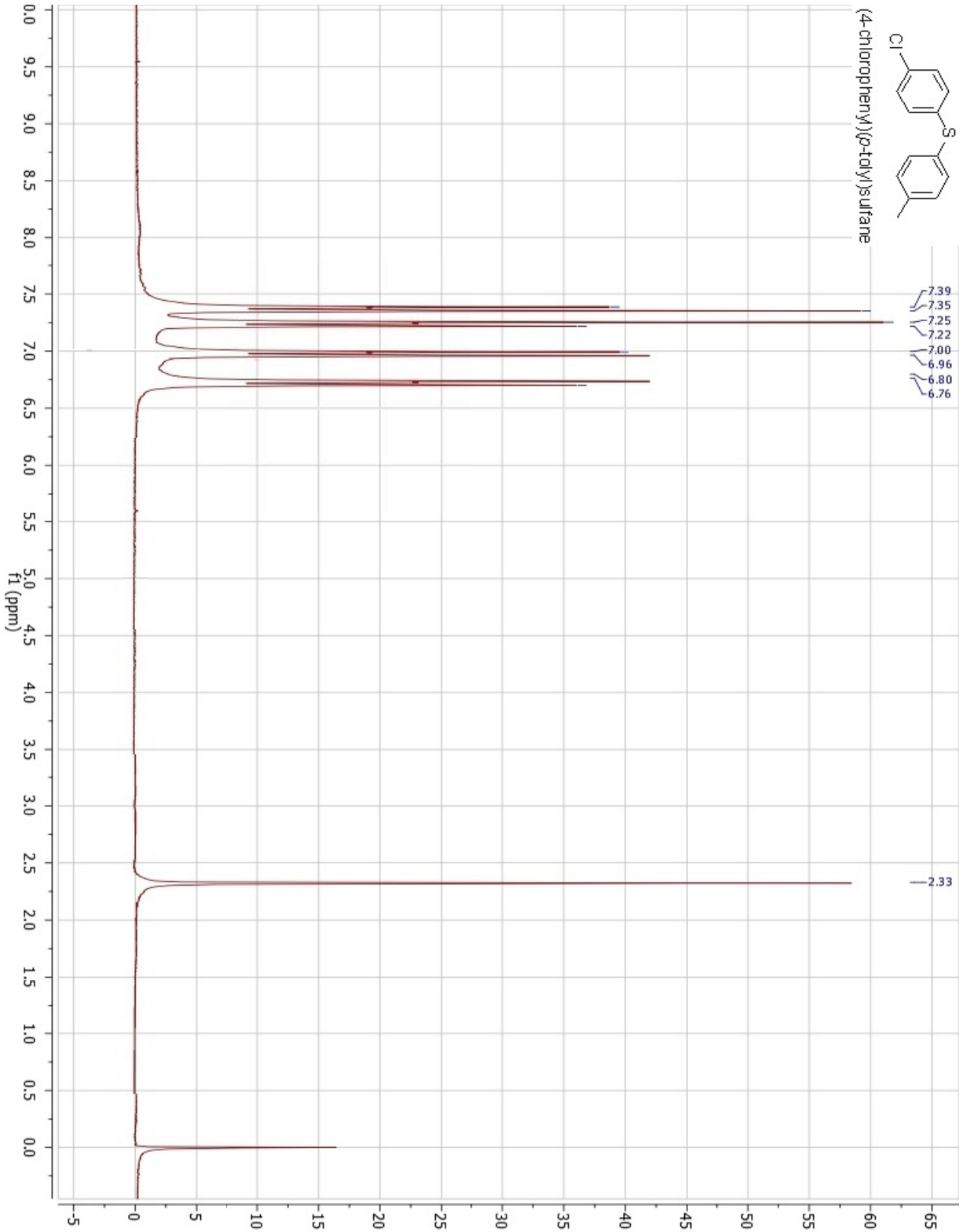

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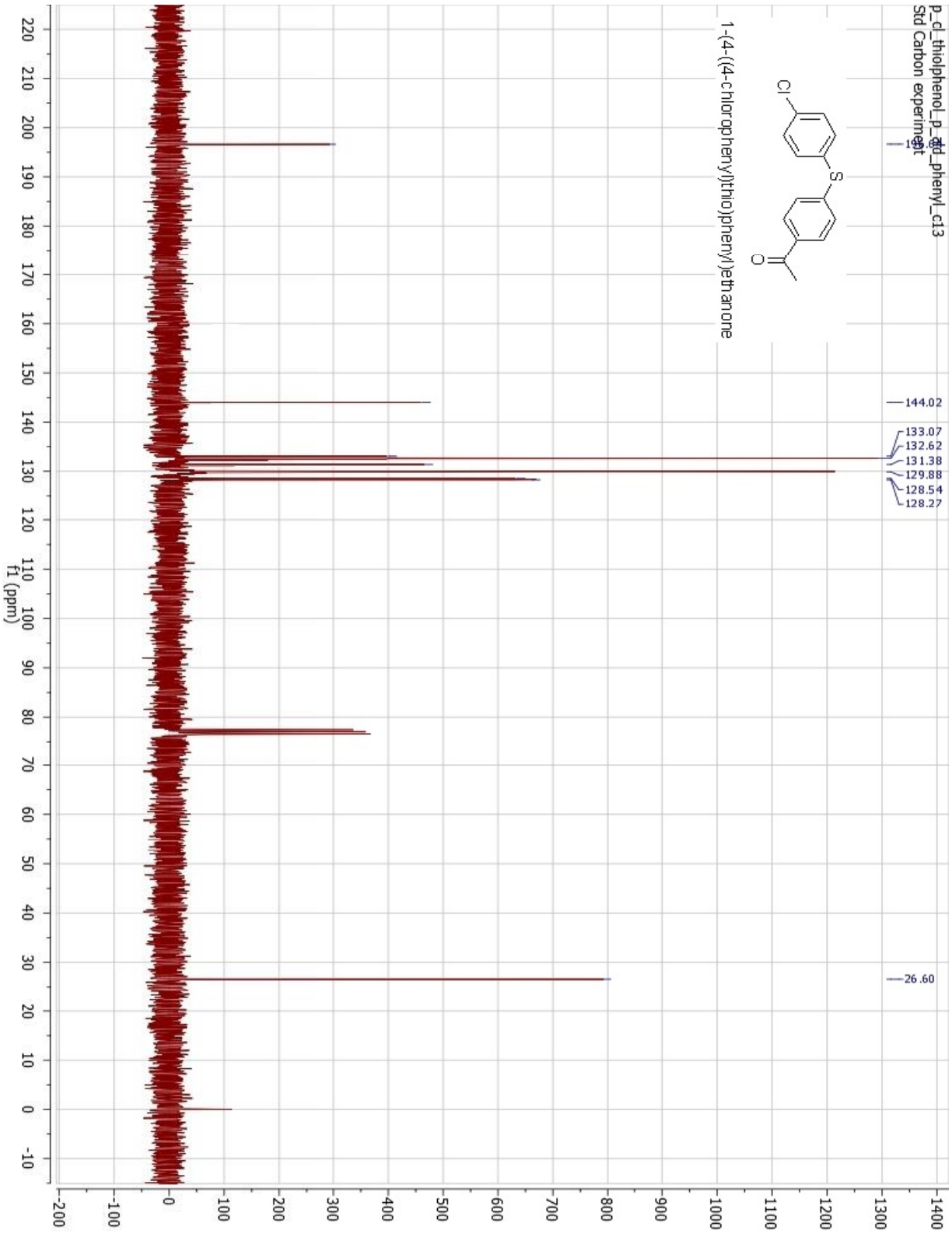

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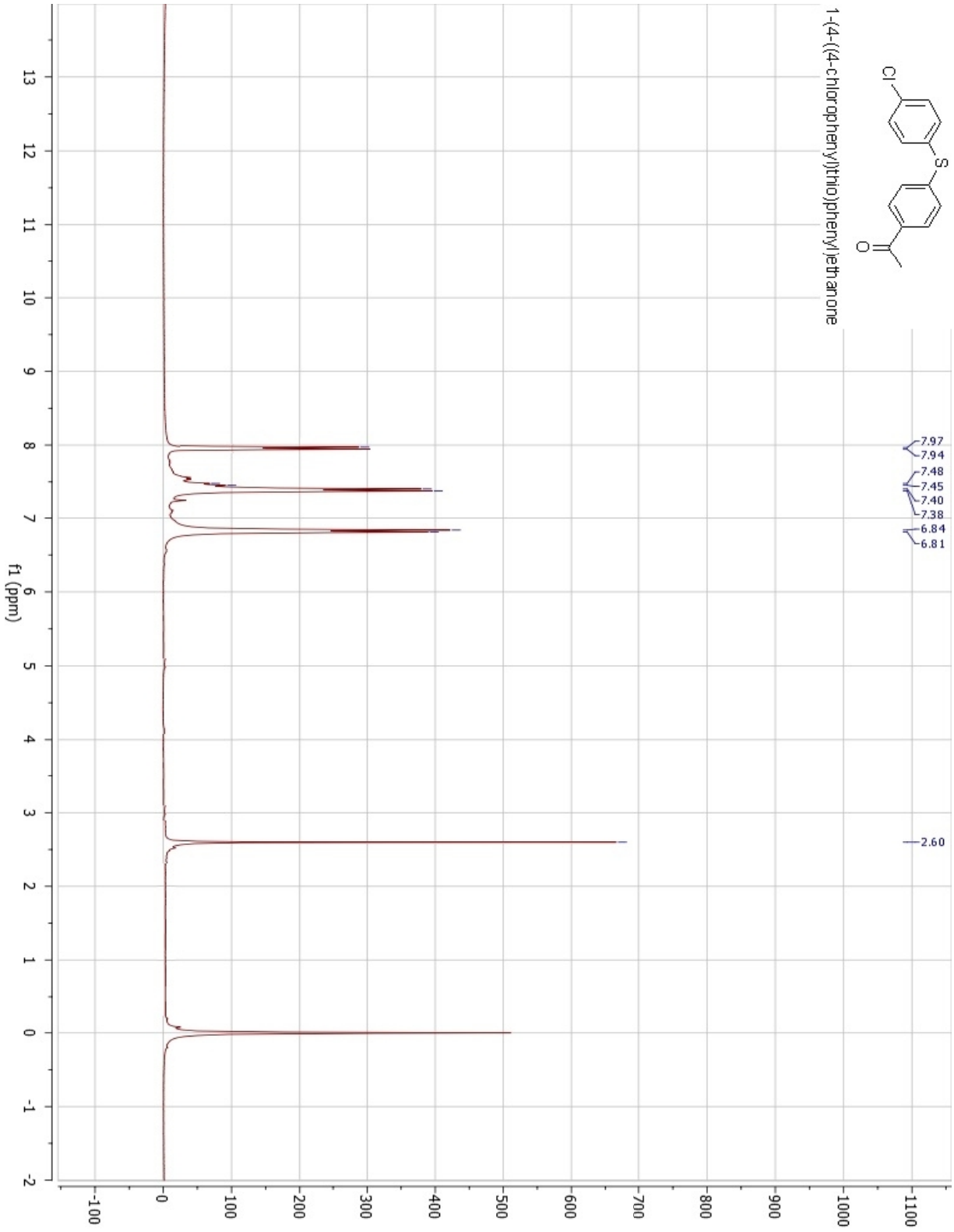

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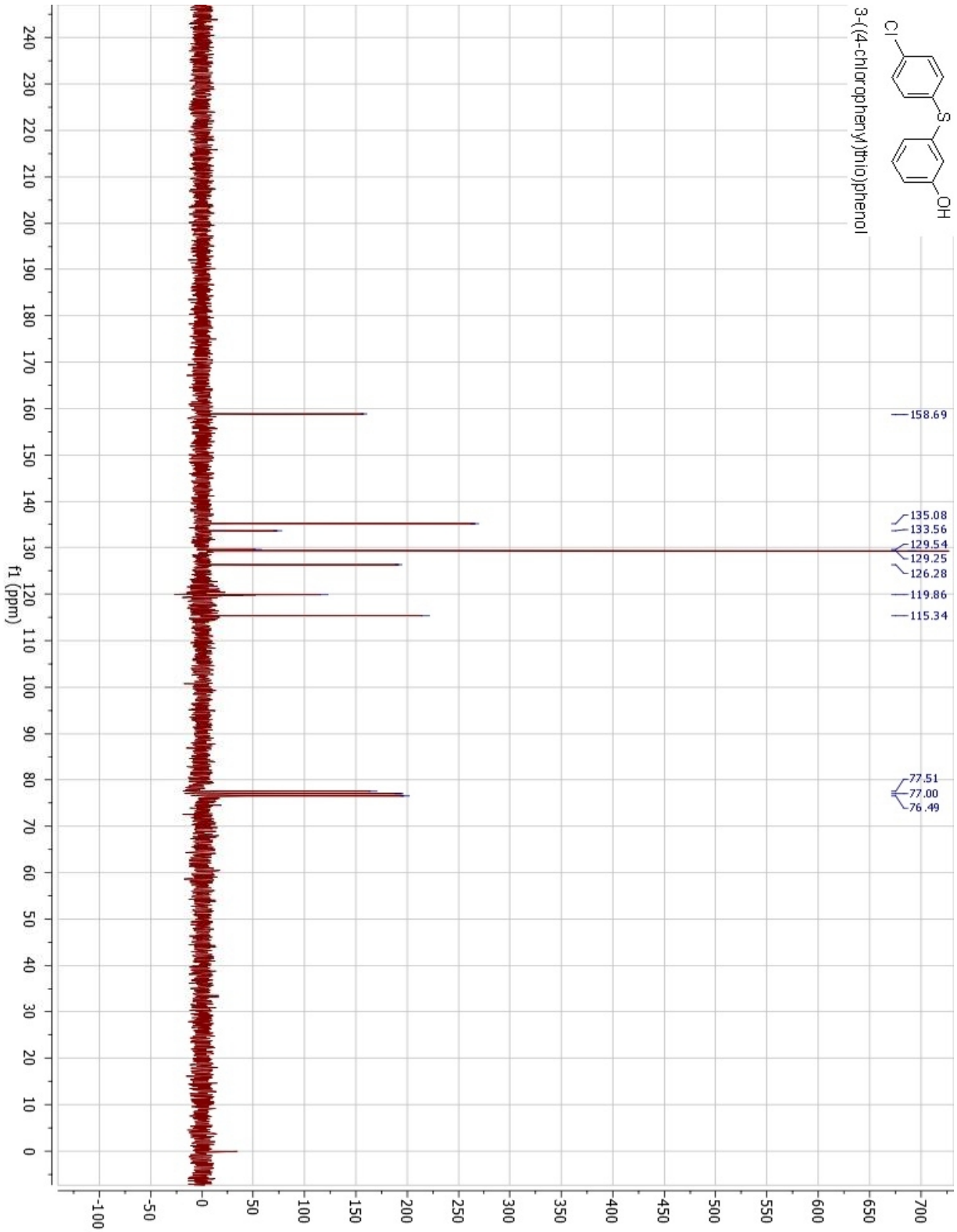

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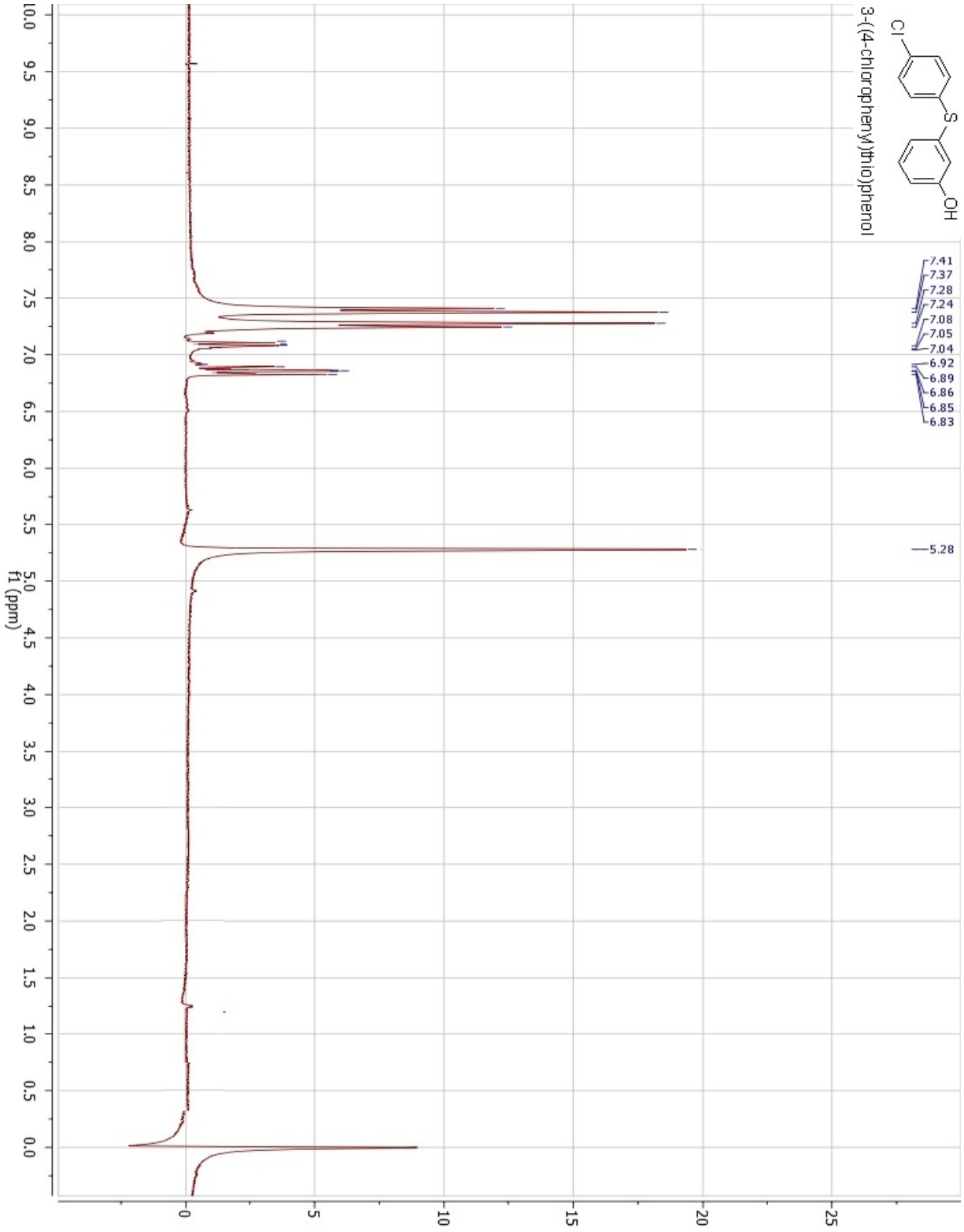

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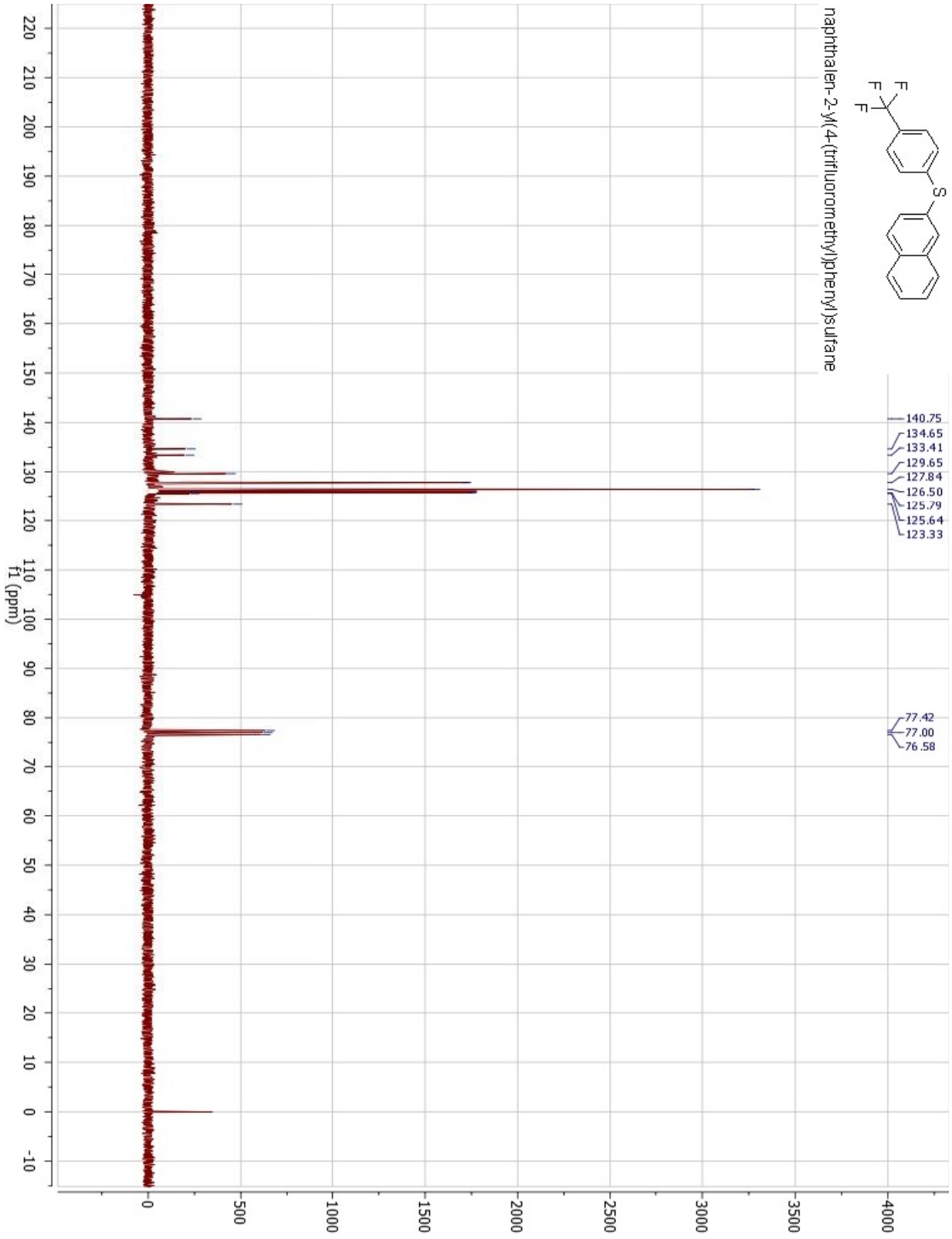

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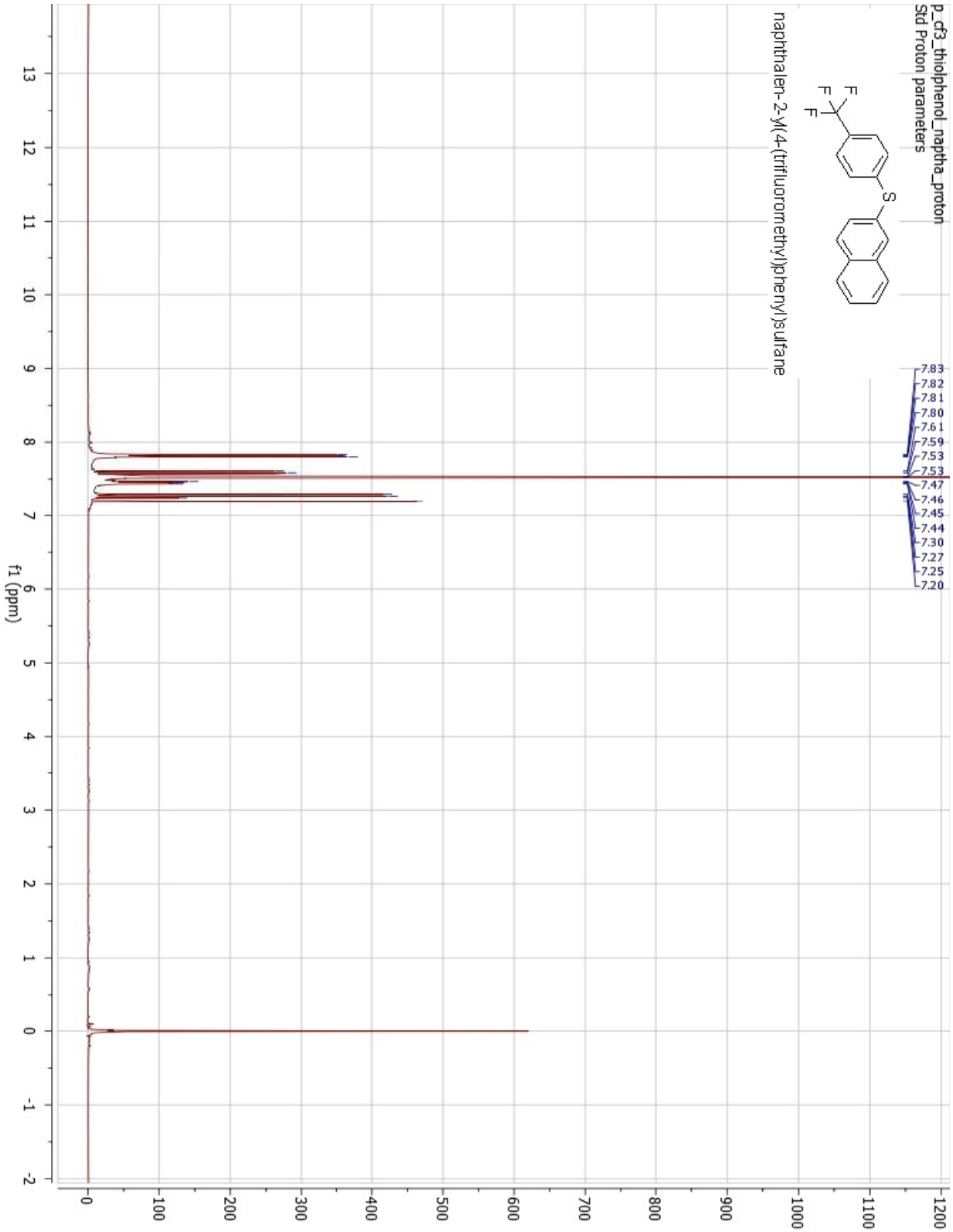

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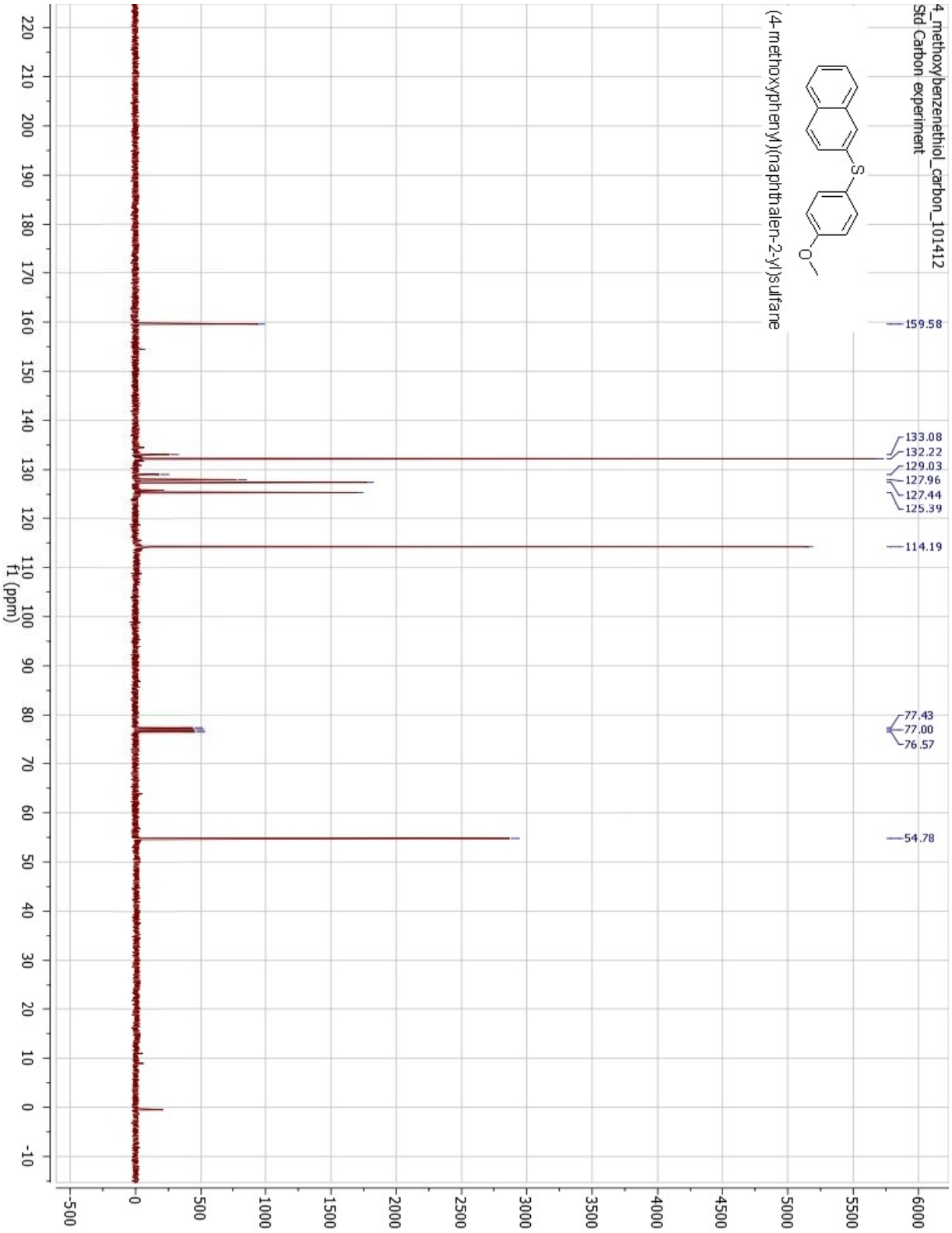

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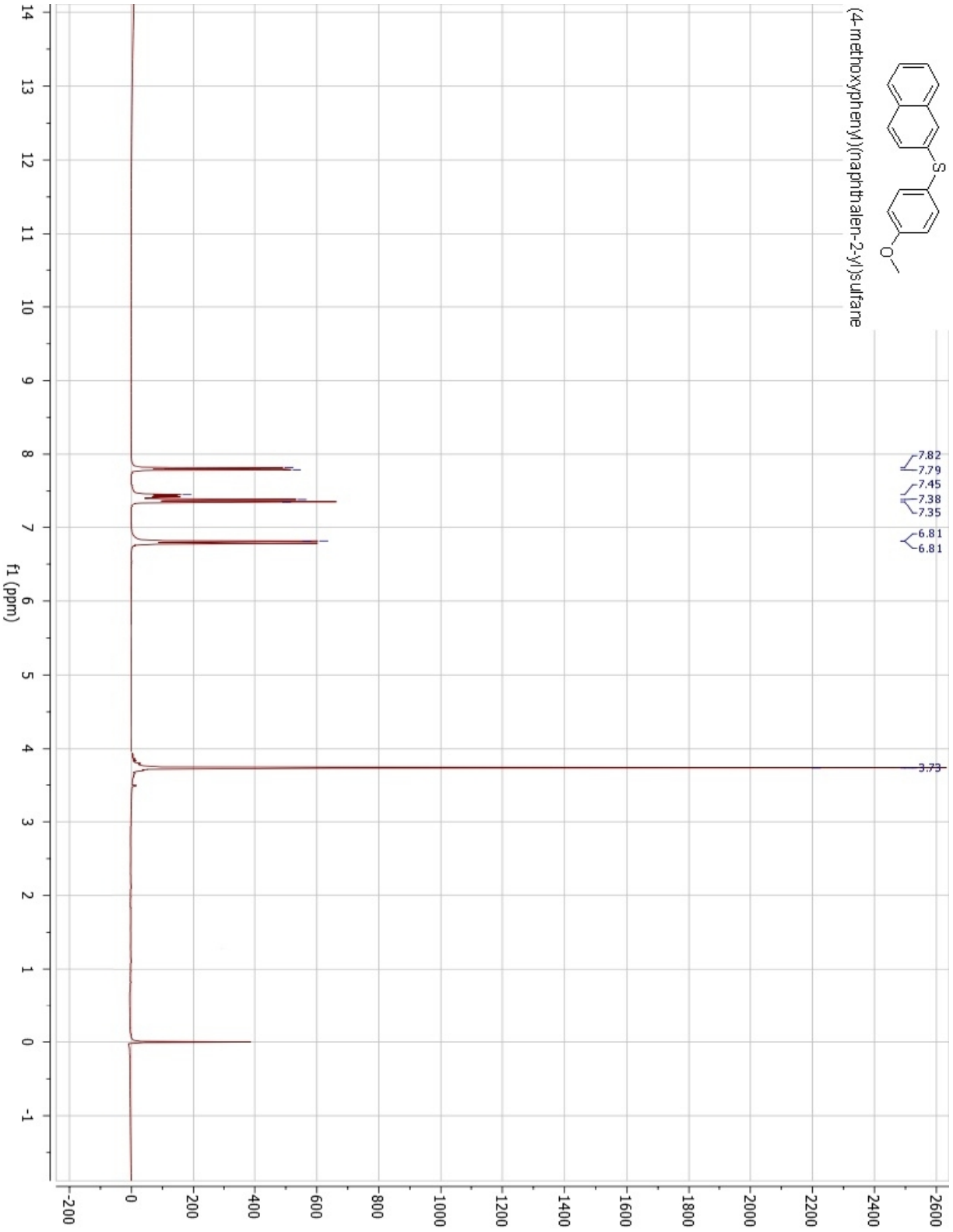

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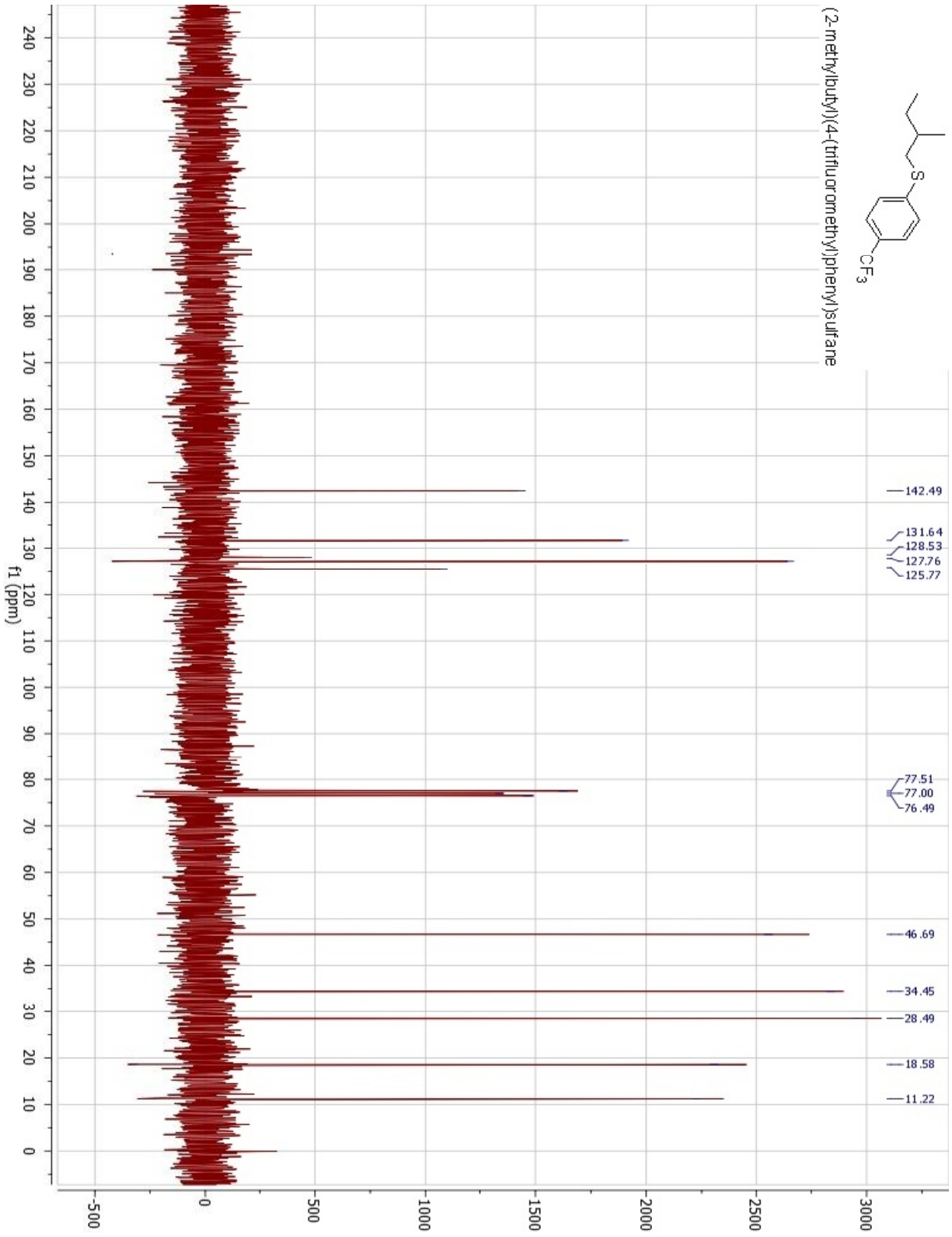

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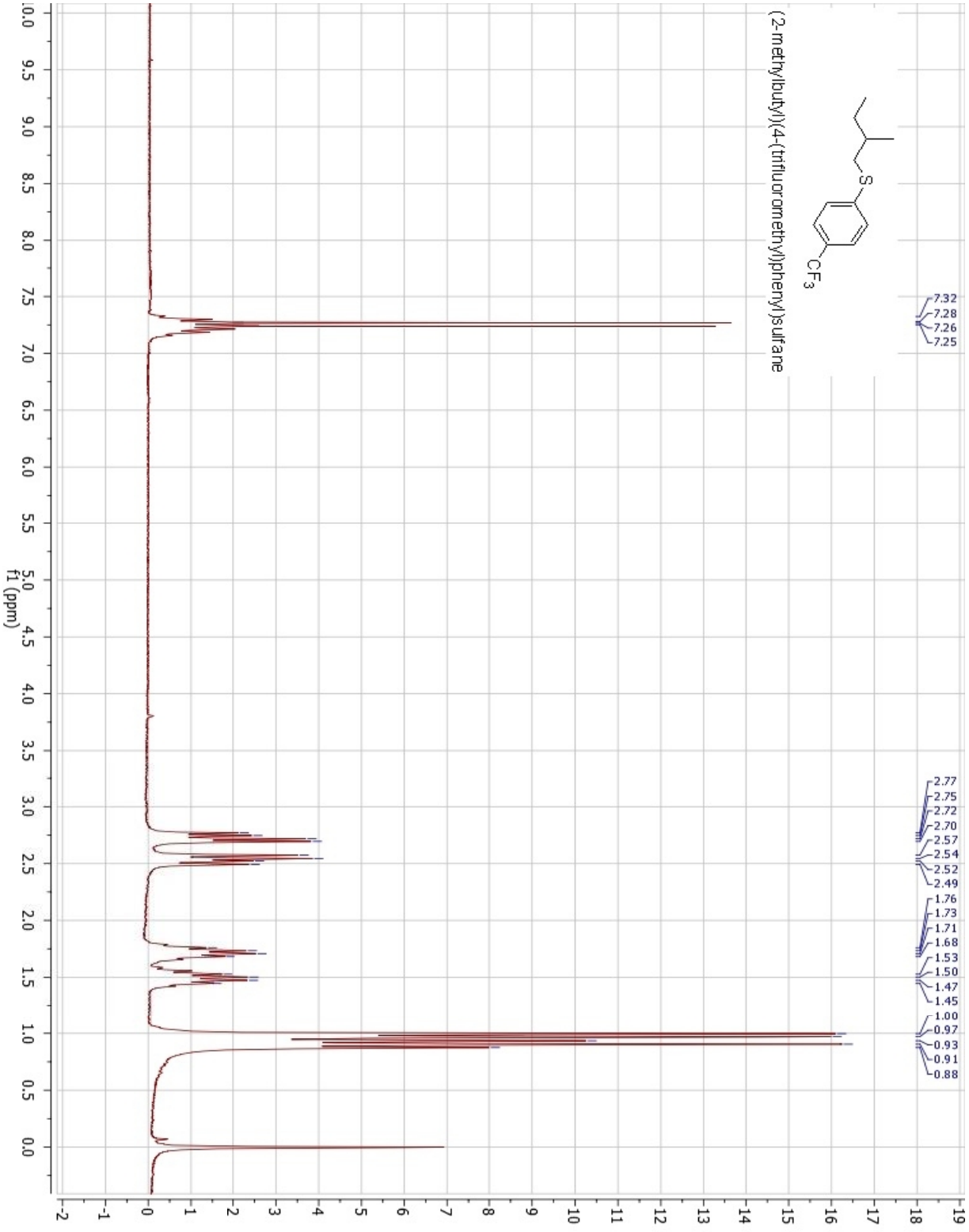

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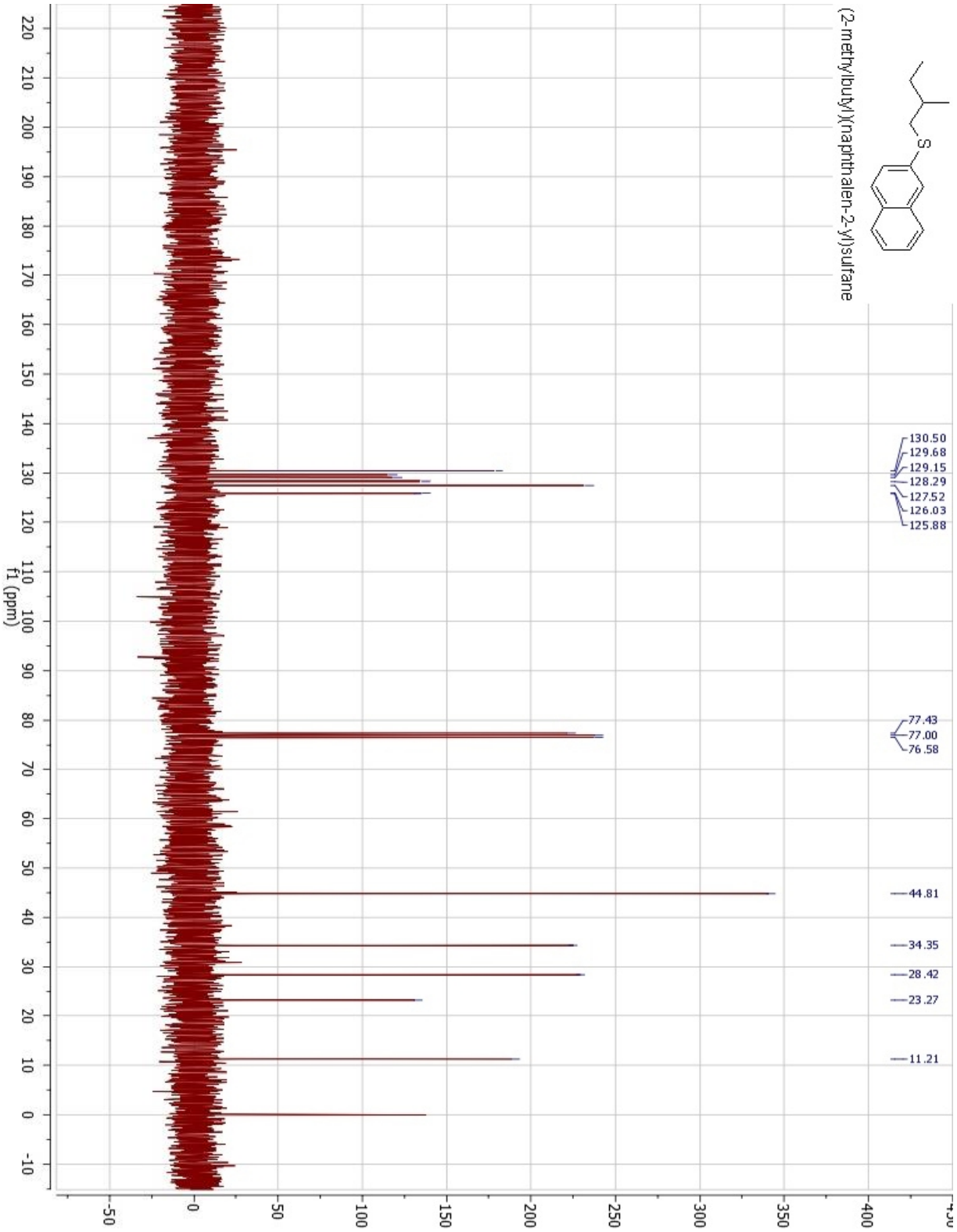
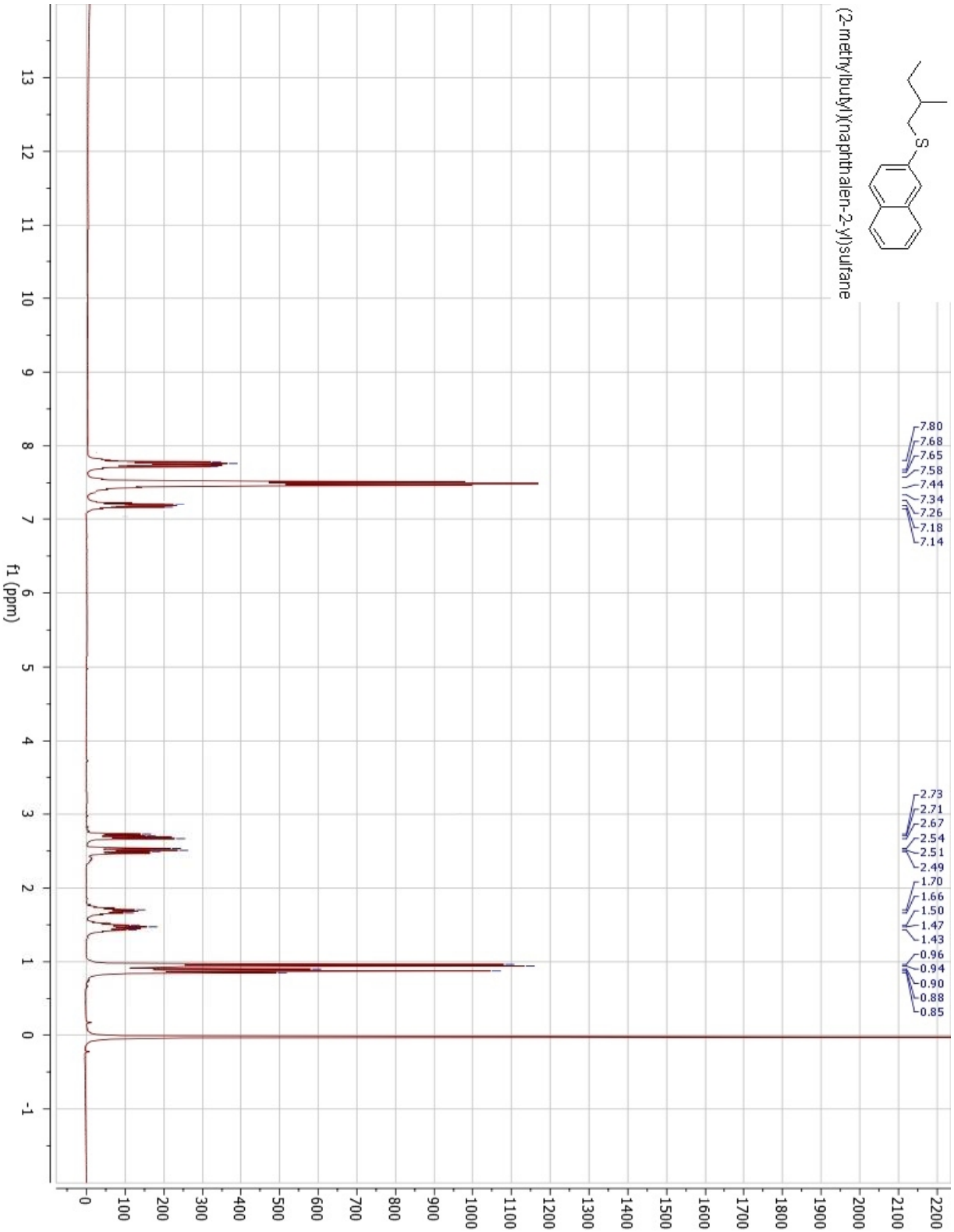
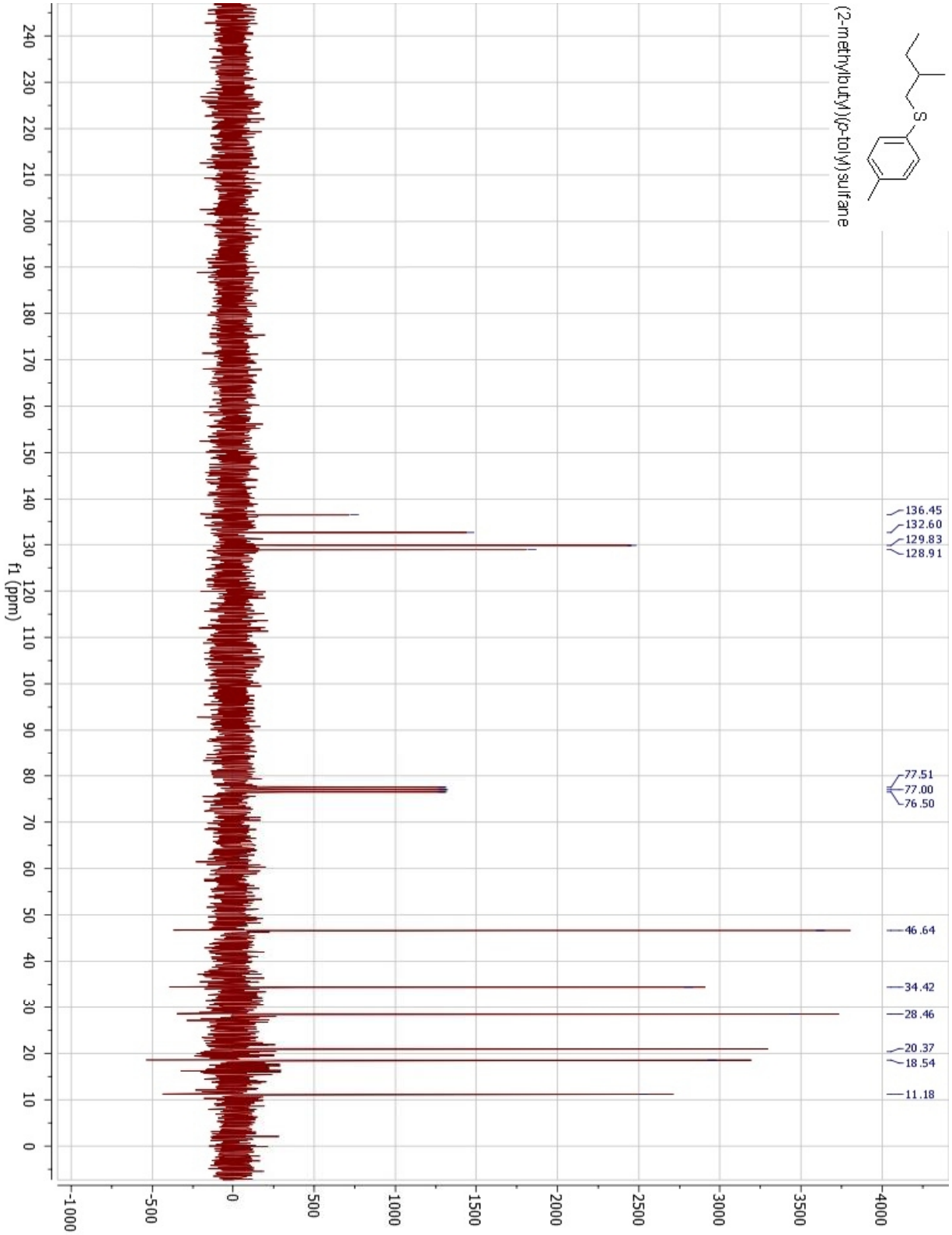


[1]Hydrogen NMR



^{13}Carbon NMR



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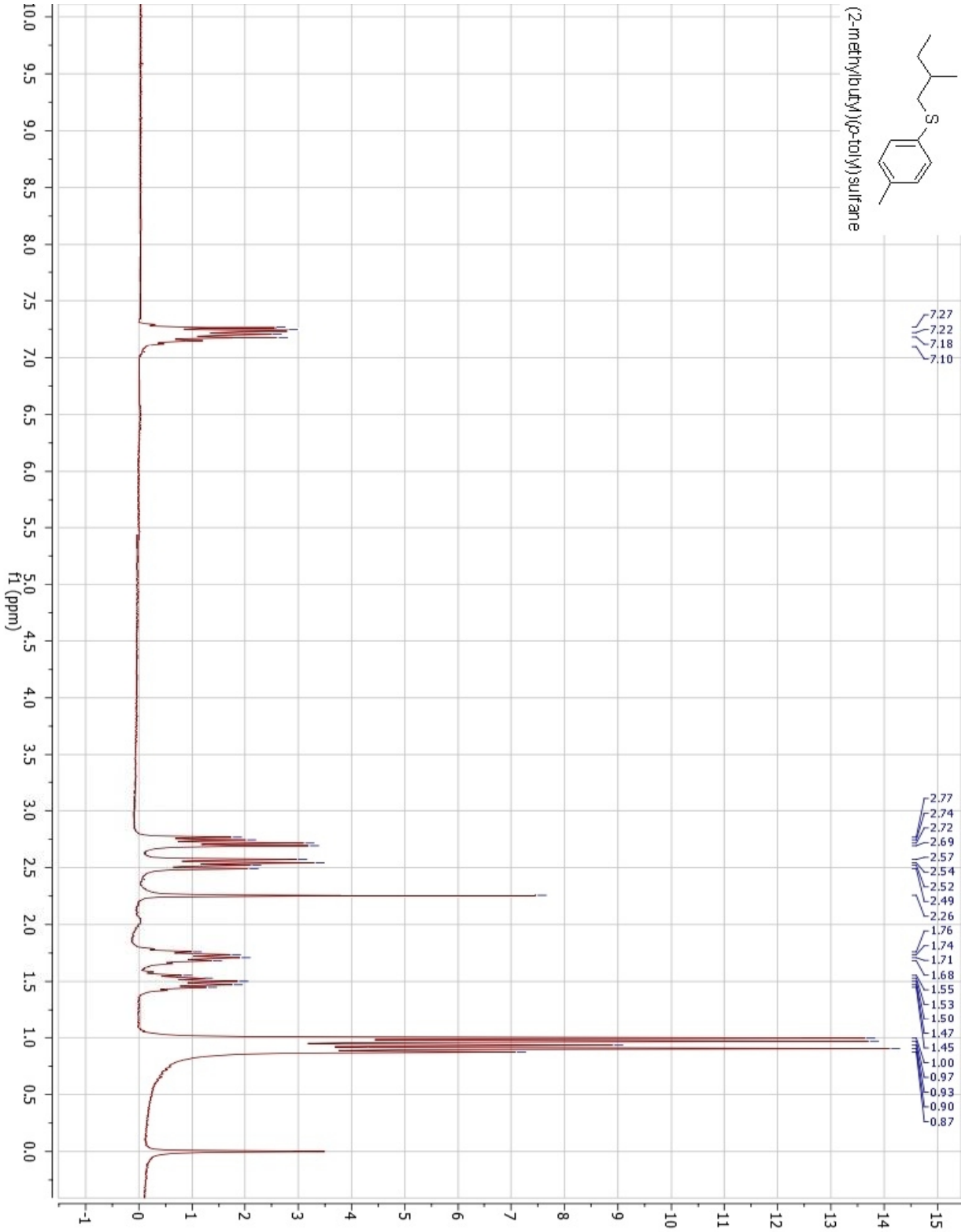

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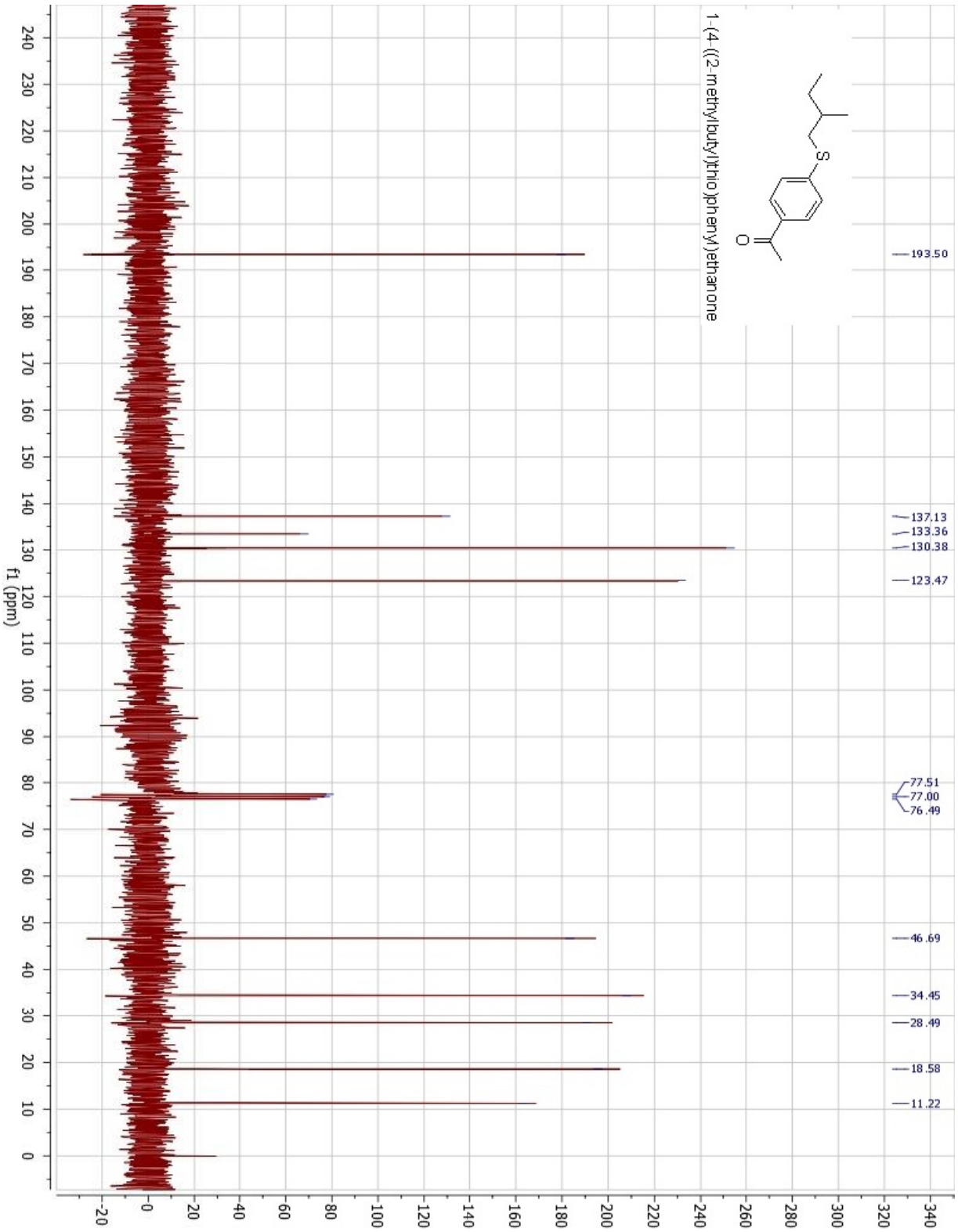

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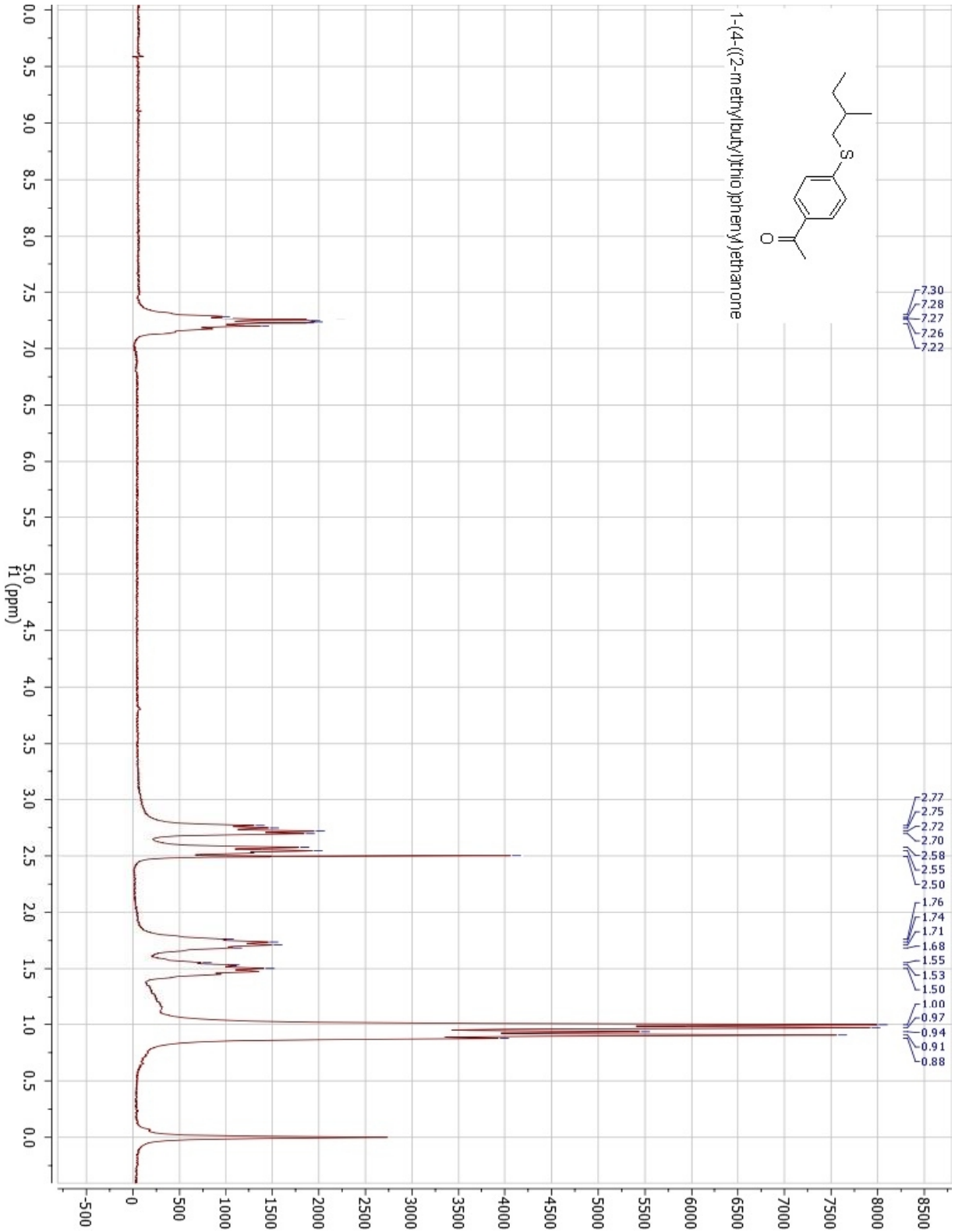

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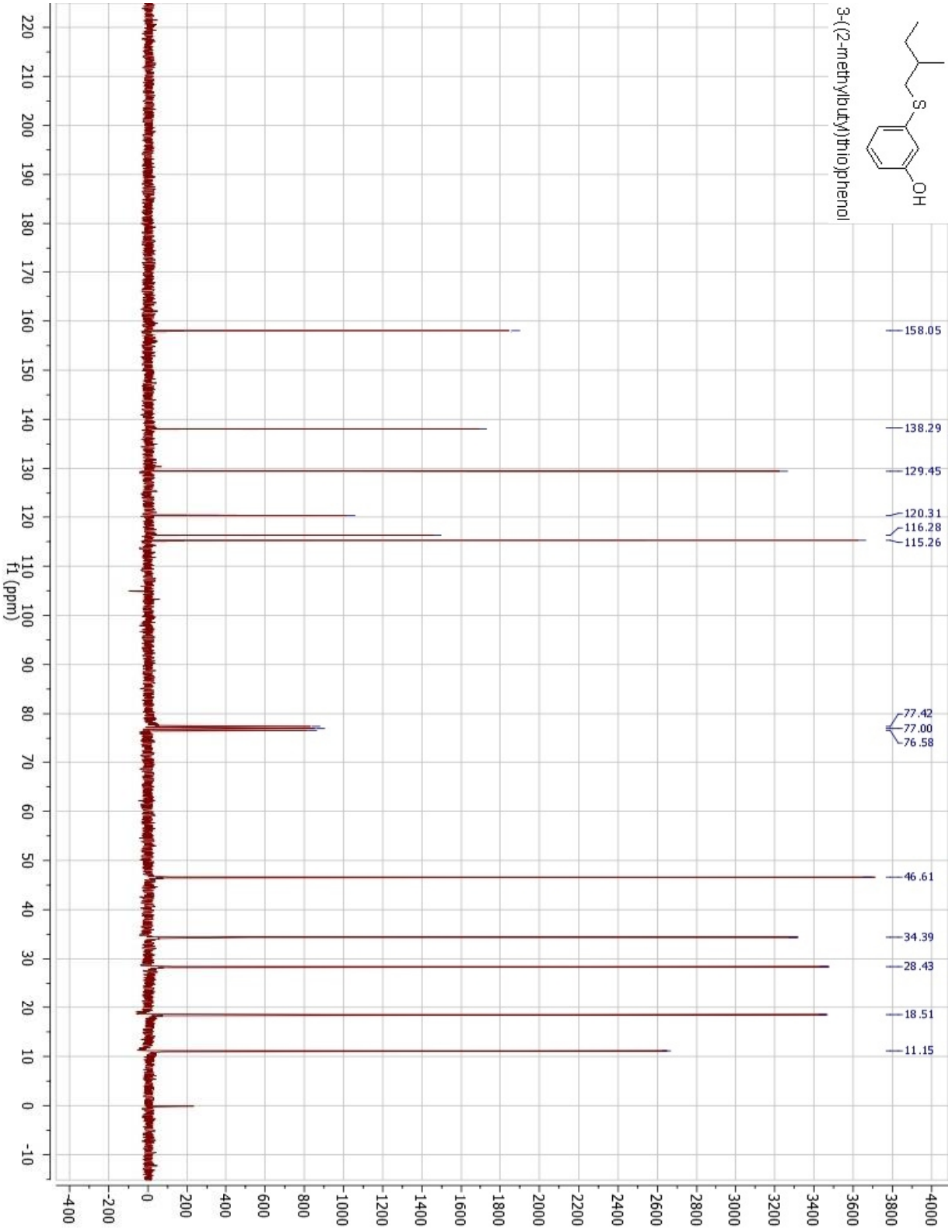

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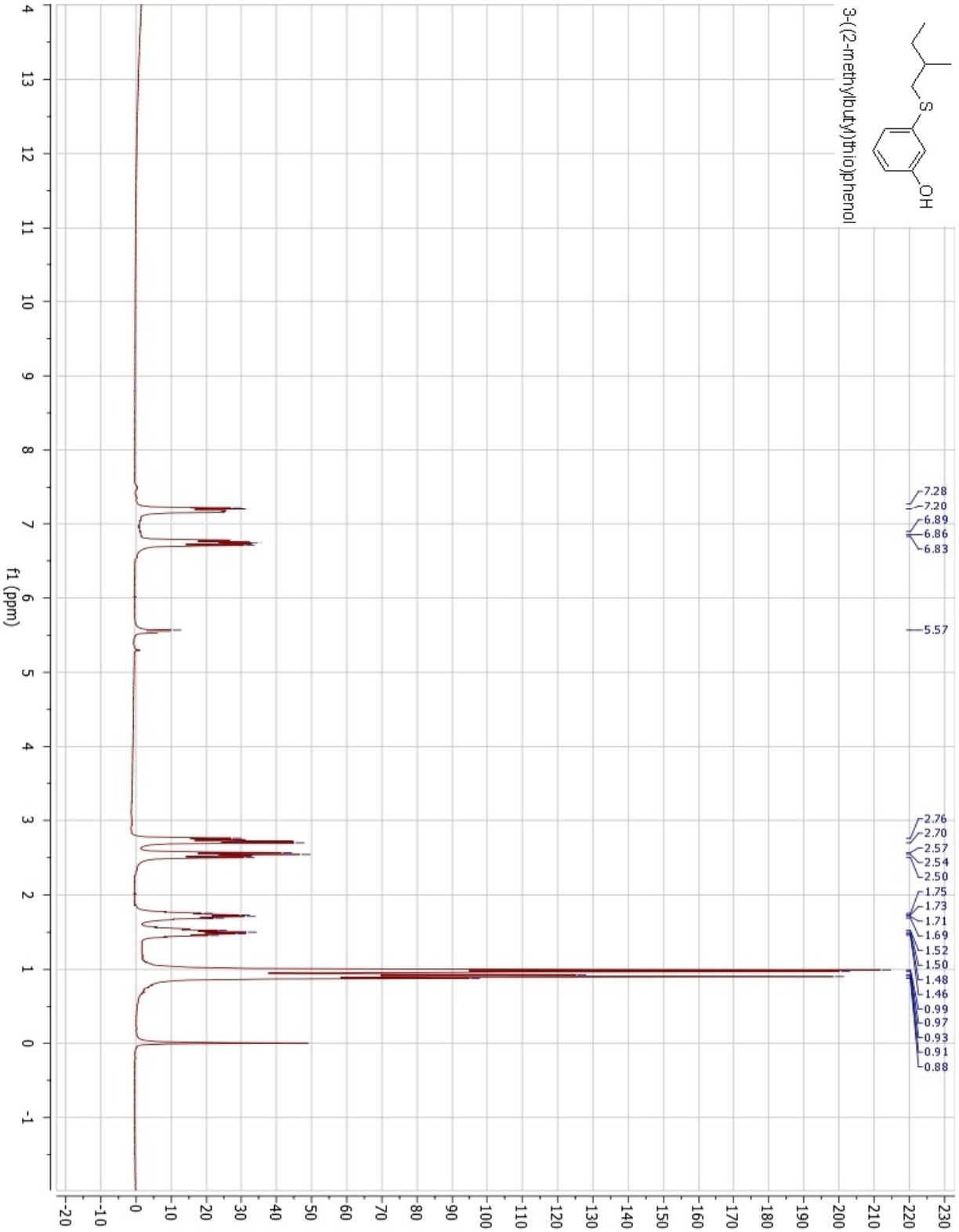

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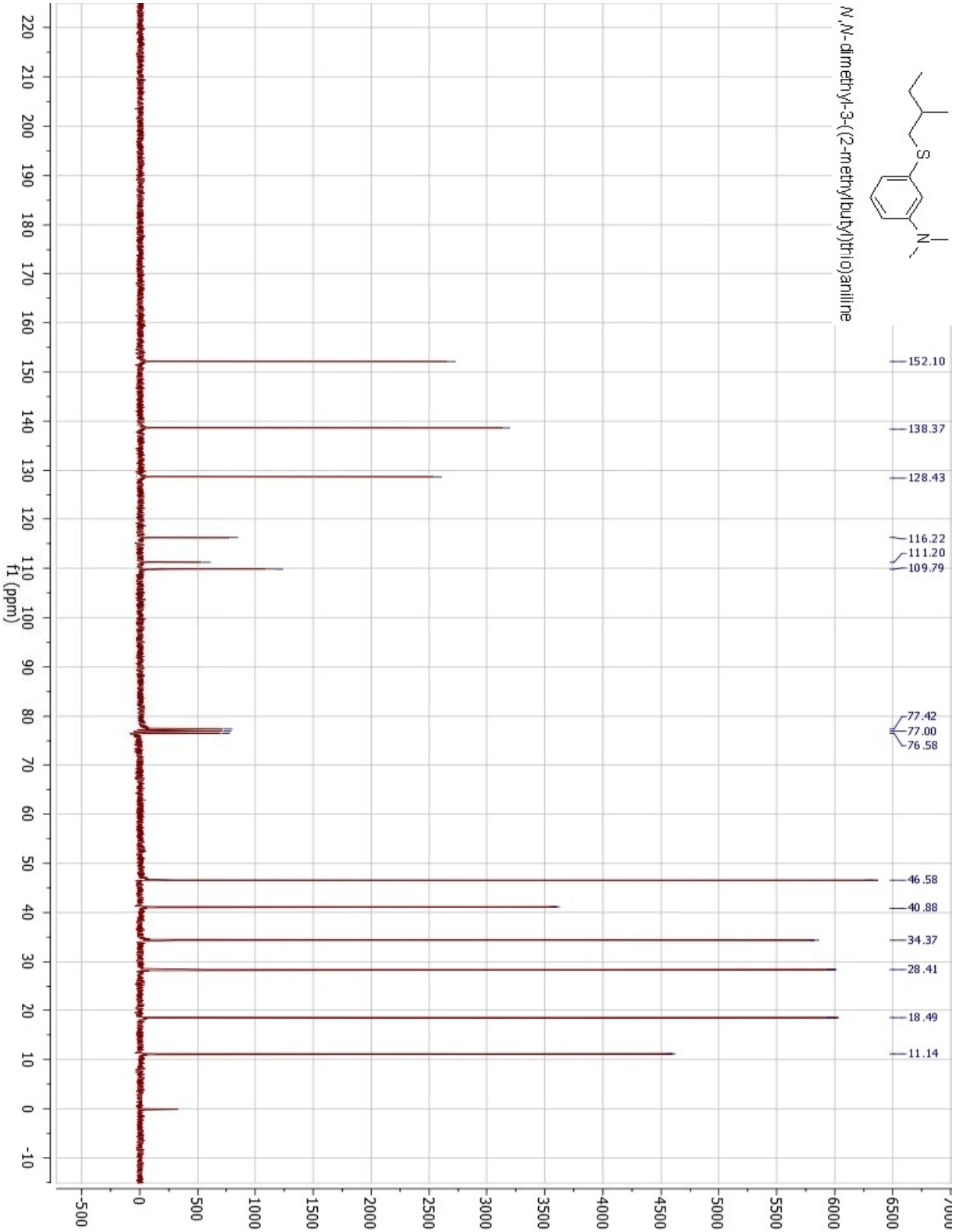

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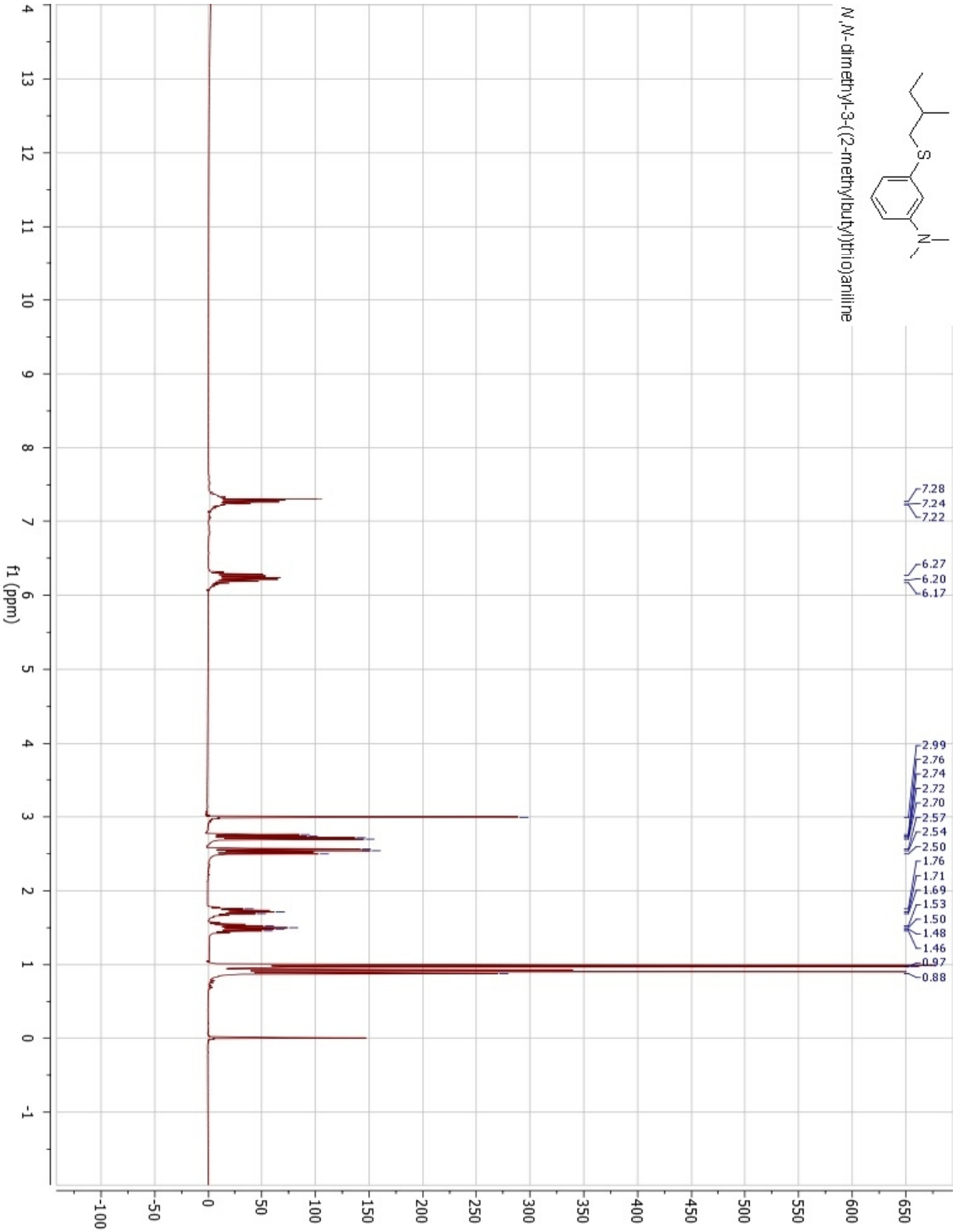

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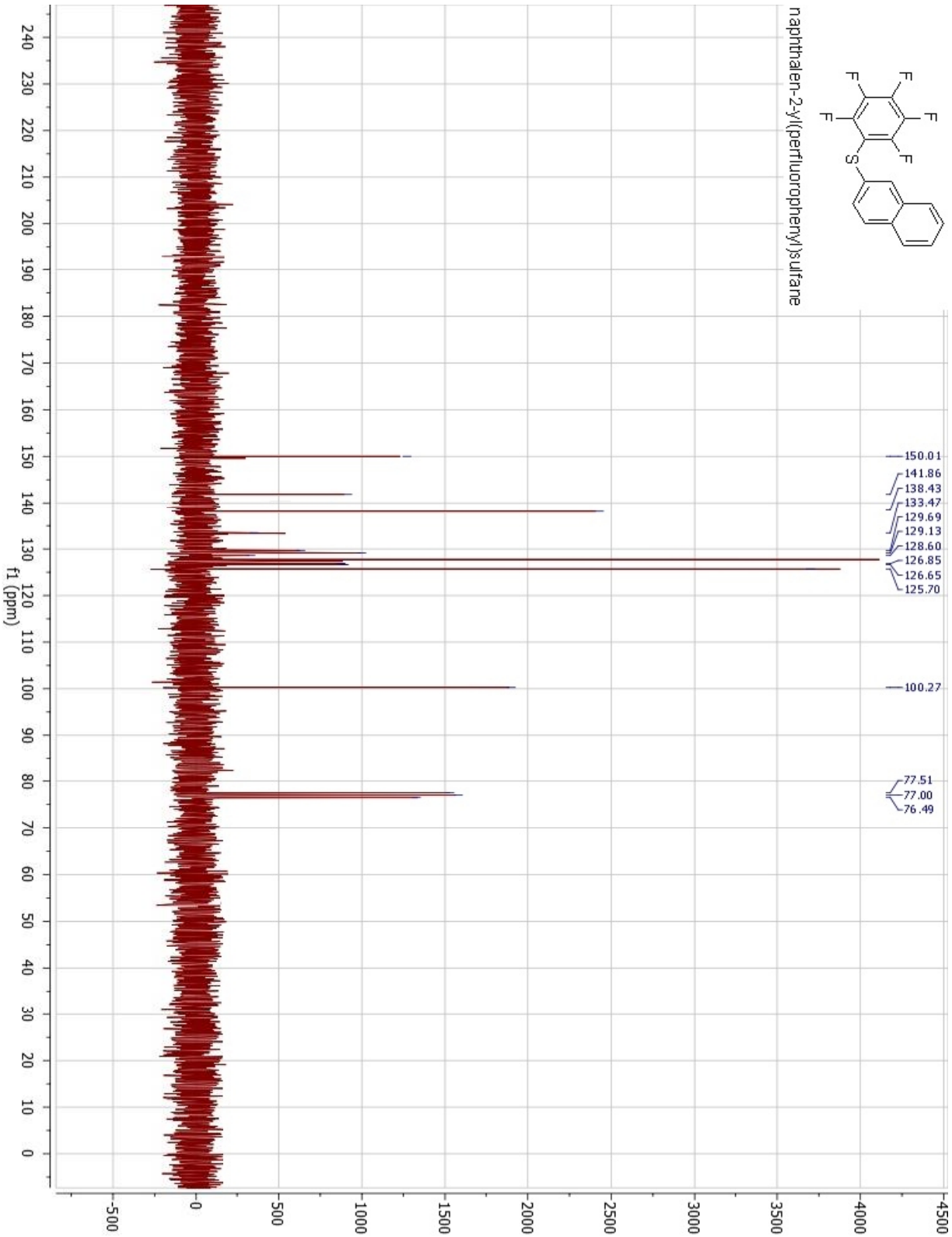

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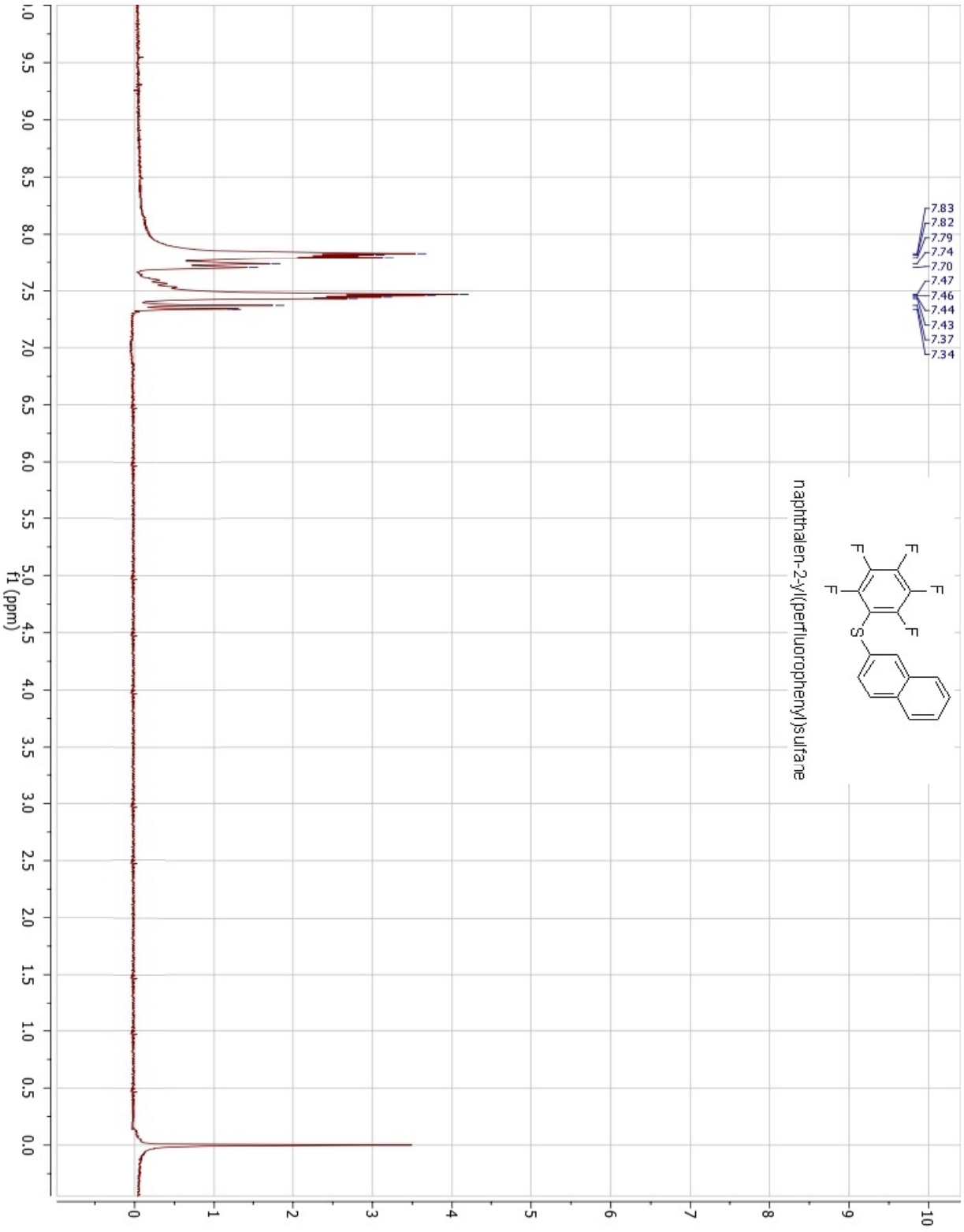
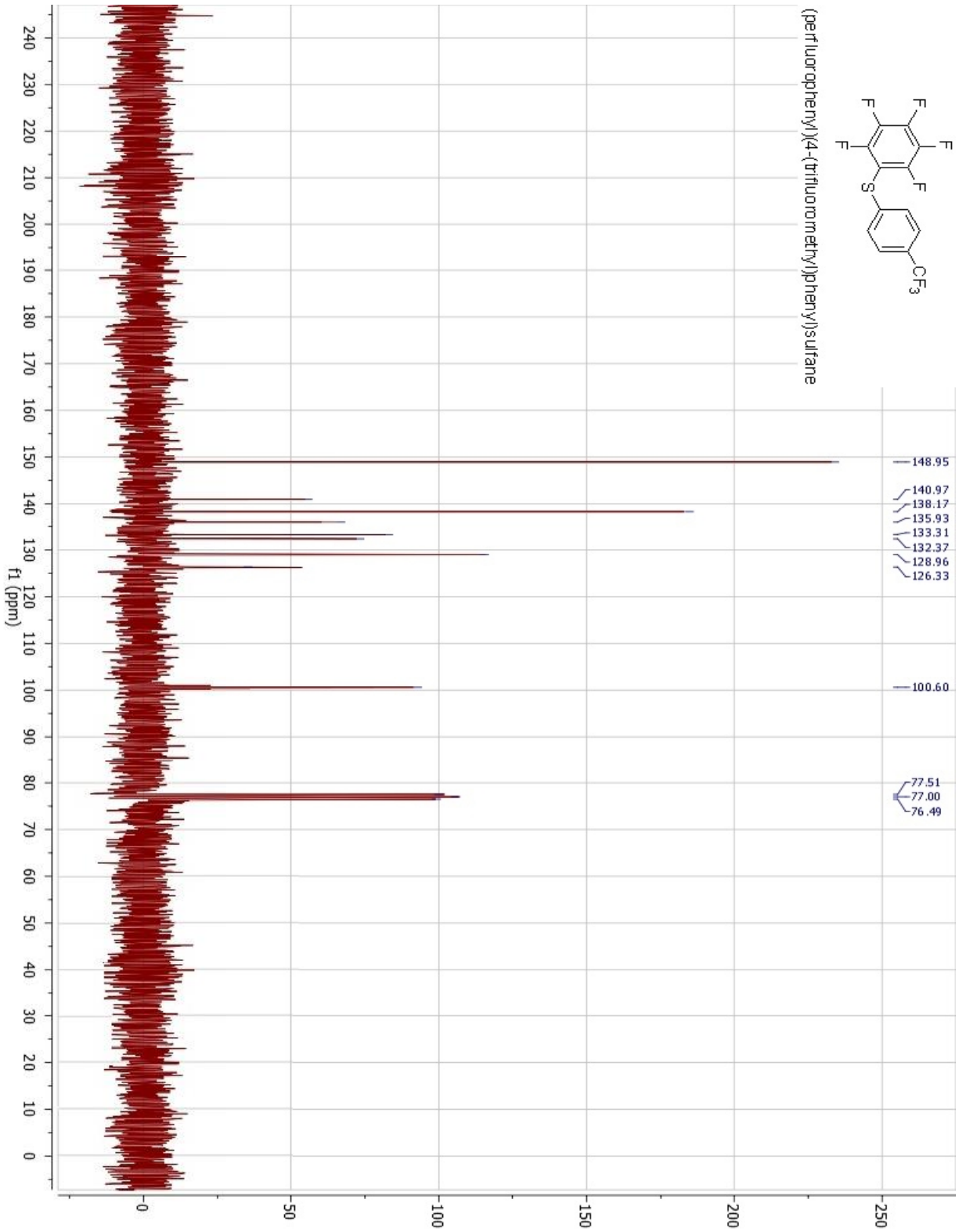


^{13}Carbon NMR



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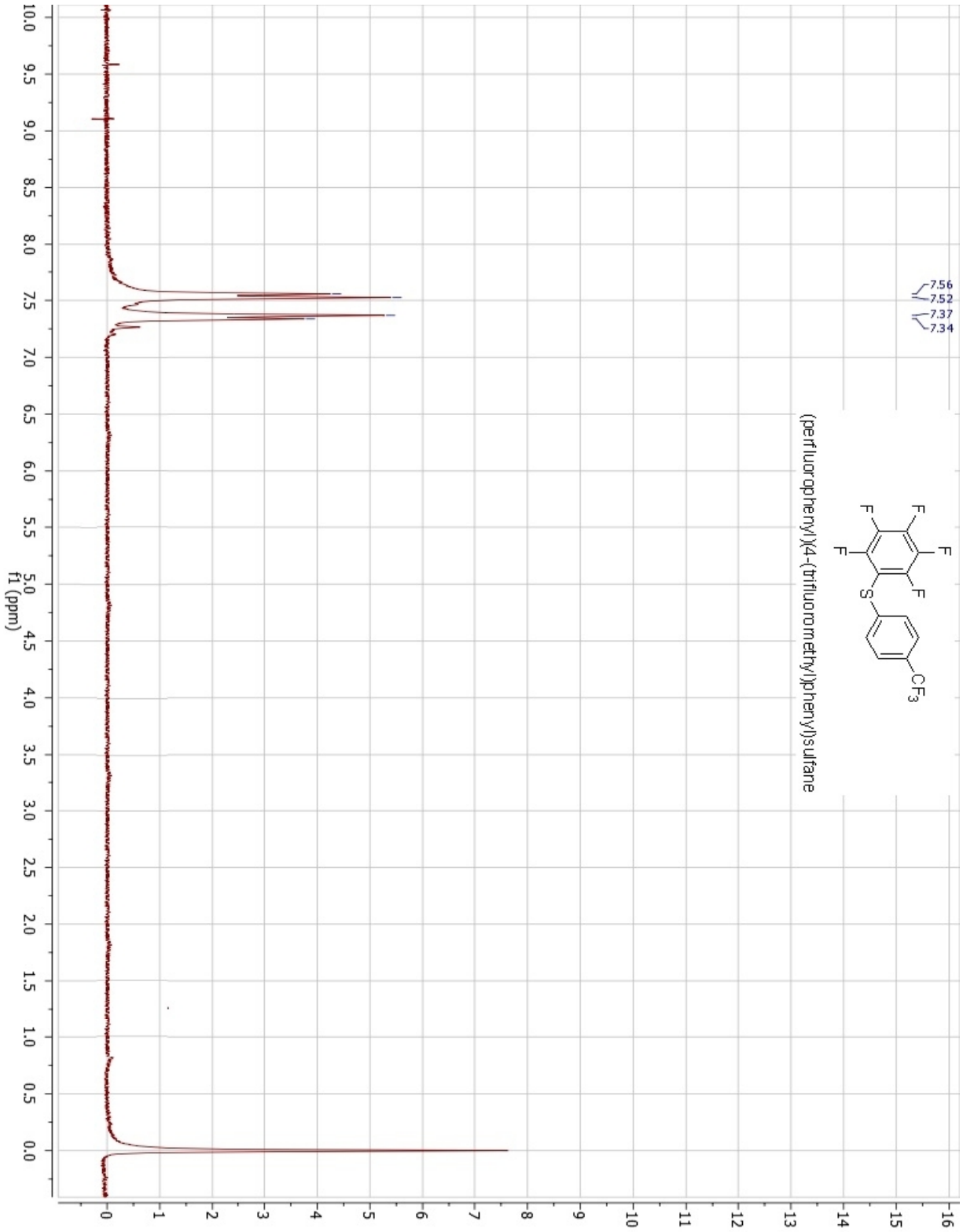
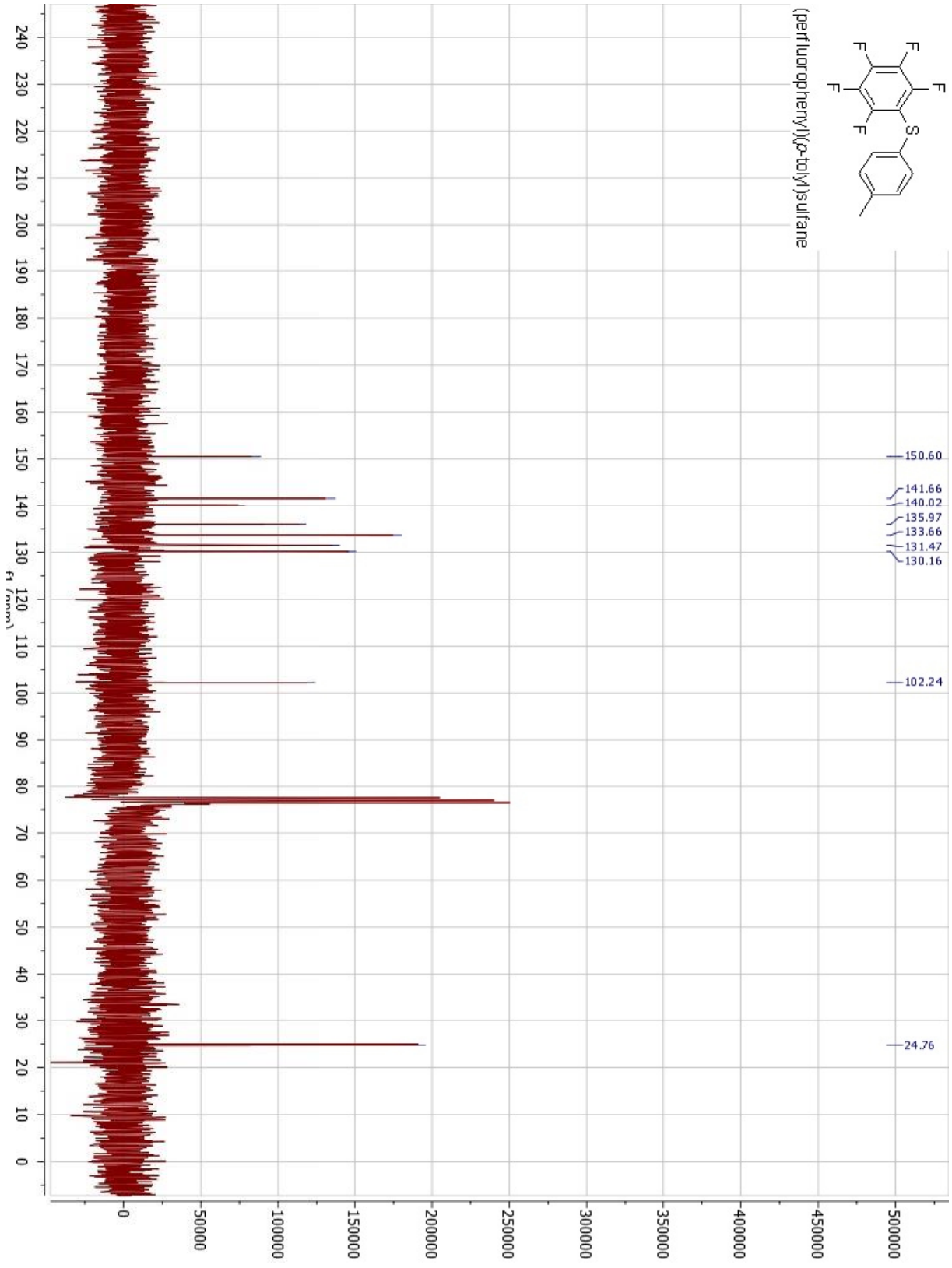


^{13}Carbon NMR



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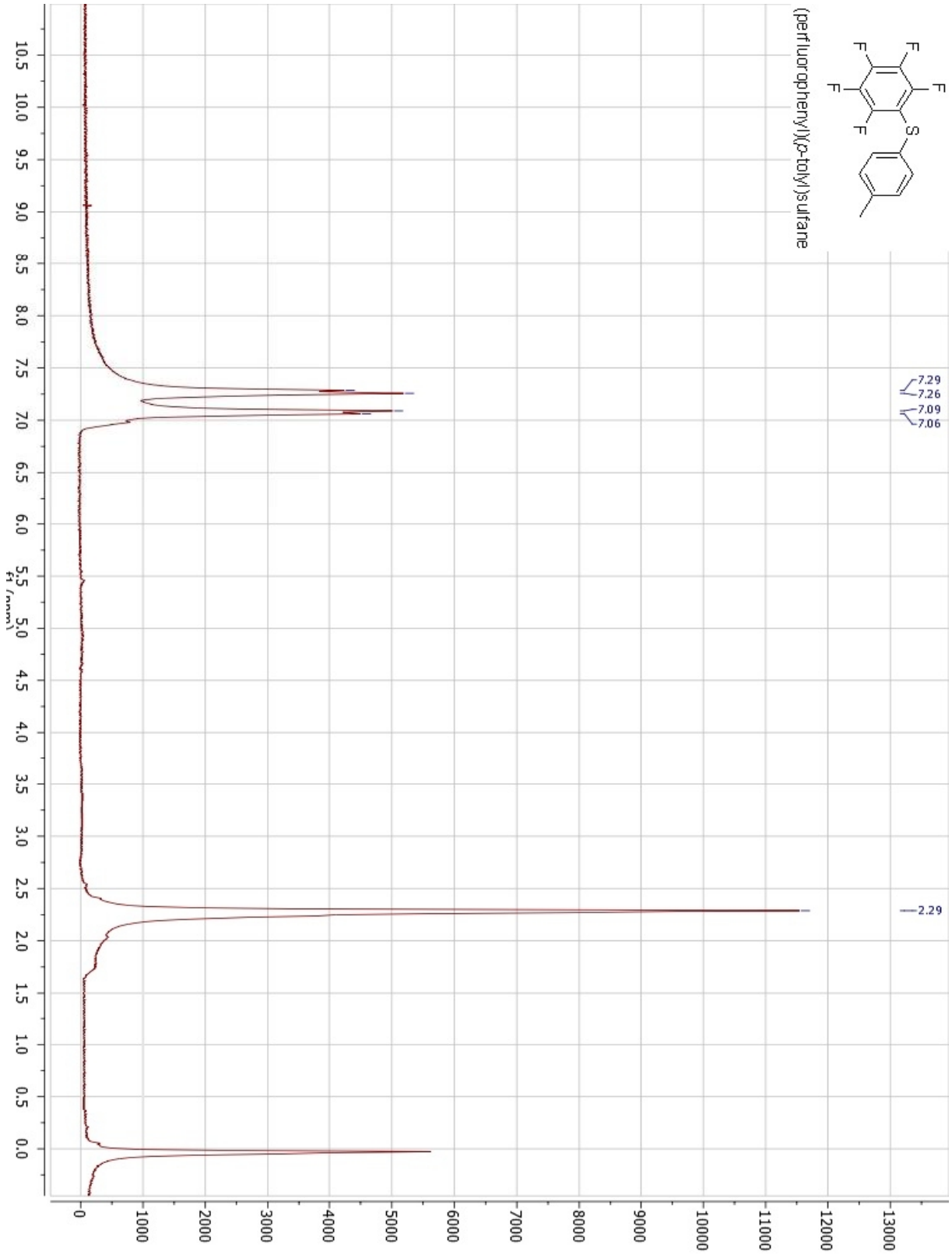

VITA

Bryan J. Musolino was born on 19 September, 1972, in New Kensington Pennsylvania. After graduating in 1995 with a Bachelor of Science degree in chemistry from Indiana University of Pennsylvania, he gained employment with USX Corporation as an industrial hygiene and environmental safety chemist. In 1998 he went to work for Microseeps Inc. Environmental Consulting as a risk analysis chemist. In the summer of 2001 he started work as an emergency medical technician with Tri-Community South EMS, while simultaneously enrolling at Indiana University of Pennsylvania to complete his Masters of Science degree in chemistry. While with Tri-Community South EMS, he assisted in the recovery operations of Flight 93 in Shanksville Pa. Upon completion of his M.S. degree in the fall of 2003, he was commissioned as a Second Lieutenant in the United States Air Force. In February of 2004 he arrived at his first assignment at Wright Patterson Air Force Base, Warner Robins Detachment 3, Air Force Petroleum Office (AFPET). While there he served as the lead petroleum chemist, with the prime role of performing investigative analysis to identify and resolve flight and ground support system malfunctions and failures. Amongst numerous cases of fuel contamination, ground system failures, and airframe malfunctions, he identified a serious source of jet fuel contamination. This identification led to his design of a detection sensor and the publishing of the paper titled "Detection of Super-Adsorbent Polymer in Jet Propulsion Fuel using a Sodium Ion Selective Electrode," in the ACS journal Energy and Fuels. Also during this assignment he completed his first deployment to southwest Asia, assigned to the 379 Air Expeditionary Wing, where he was responsible for the quality assurance of all aircraft breathing air and oxygen, and technical assistance of any fuel related issues for the southwest Asia area of operations (AOR). When he returned from the deployment in the fall of 2005, he was transferred to the Disruptive Technologies Branch of the National Air and Space Intelligence Center (NASIC). He was

promoted to the rank of First Lieutenant, and given the assignment of an advanced materials technology analyst. This position enabled him to uncover several chemical, biological, and anti-material warfare efforts by hostile countries, which garnered top level Congressional, Department of State, and Department of Defense attention and the implementation of new counter measures by the U.S. Air Force. Amongst these counter measures was a $200K program which he personally managed for the identification of a portion of the threat agents. Additionally, he was recognized by several intelligence agencies for his work in identifying adversarial low observable technology and research on disruptive communication and radar programs. In the spring of 2008 he was promoted to Captain, and transferred to the 709th Nuclear Systems Squadron of the Air Force Nuclear Weapons Center in New Mexico. Shortly after his arrival, he was deployed to Iraq with Combined Joint Task Force Troy as the officer in charge of the counter-IED, human targeting program. Within this program he was responsible for a 43 man team embedded throughout Iraq, and $380K in government assets. The team he led, and efforts he directed, were responsible for the targeting of 450 terrorists and insurgents, with 225 captured or killed, including 95 high value individuals, and disruption of an attack on the continental United States. Additionally, he implemented new technologies, for the identification of IED materials, which were capable of producing warrant quality forensic evidence; was an MRAP driver for the Task Force Troy's Personnel Security Detachment; and completed an estimated 80 combat missions. Upon returning from Iraq, he became the lead chemical analyst in the 709th Nuclear Systems Squadron, with responsibilities in counter-CBRNE offensive operations, consequence management, threat identification, and sensor development. Amongst these responsibilities he successfully managed a $500K sensor development and deployment project, new chemical neutralization, and authored a

comprehensive intelligence and science assessment of future chemical warfare threats. In August of 2010 he was accepted to the Air Force Institute of Technology, at the University of Tennessee, to complete his Doctor of Philosophy in Organic Chemistry. While working on the degree, he published the paper titled "Ultrasound Induced, Copper Mediated Homocoupling using Polymer Supported Aryltrifluoroborates," in Tetrahedron Letters. August 2013 saw him finish the degree, be promoted to the rank of Major, and transferred to the 711 Human Performance Wing at Fort Sam Houston in San Antonio Texas.